RADIOLOGY

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RADIOLOGY

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Relative Biological Effectiveness: A Symposium[1]

Introduction

TITUS C. EVANS, Ph.D, Moderator

THIS SUBJECT of relative biological effectiveness (RBE) can have either a broad interpretation or a restricted, more specific one. In the broad sense, for those who are interested in protection primarily, the important thing is to know the relative effectiveness of the end-result, the mechanism being of a lesser importance. But those of us concerned with the more fundamental aspects of the problem are interested in the specific action, and we hope ultimately to learn something more about the biologic effect of radiations. We are interested in the action also because of what we can learn about the particular biologic unit that may respond differently to one type of radiation than to another. And so, if we are talking about the RBE in the restricted sense, we demand that everything be constant except the quality of the radiation, the density of ion pairs along the track of an ionizing particle. Lately, we use "energy transfer," whatever the type of transfer of energy may be. It is the density of *this* per micron of path that we think accounts for the difference in RBE. Of course, our unit (for dosage purposes) is a gram of tissue, and within a gram of tissue there can be a lot of variation, but we are thinking in terms of density changes per micron along the path of an ionizing particle.

So you will see the different interpretations in the papers that are to follow. None of us, of course, is able to say exactly that we are comparing two radiations in which the intensity is the same and the depth dose is the same, and that the volume of tissue that is irradiated is the same. We make an effort, to be sure, to get all these factors under control, but to control them all at the same time is very difficult.

[1] Presented at the Forty-first Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 11–16, 1955.

The Relative Biological Effectiveness of Thermal Neutrons and of the Heavy Particles from the B^{10} (n, α) Li^7 Reaction for Acute Effects in the Mouse[1]

V. P. BOND, M.D., Ph.D., O. D. EASTERDAY, Ph.D., E. E. STICKLEY, Ph.D., and J. S. ROBERTSON, M.D., Ph.D.

Although the relative biological effectiveness (RBE) of alpha or of heavier ionizing particles has been extensively studied in microorganisms, only a few attempts have been made to determine the RBE of such particles in the mammal. This is due principally to the technical difficulties inherent in obtaining total-body or large-volume irradiation of the intact animal with heavy particles with a range in tissue of the order of a few microns. The most direct approach, *i.e.*, injection of alpha emitters into the intact animal, is not completely satisfactory. The dose received by the tissues cannot be determined accurately because of the uncertain biological half-life of the injected material, the non-uniform and changing body distribution of dose as it is being administered, and the protracted and changing rate of dose administration to the various tissues. It is possible, by delivering total-body thermal neutron radiation to mammals previously injected with a capture element such as boron or lithium, to obtain irradiation of the tissues with the heavy recoil particles liberated instantaneously in the capture process. It was the purpose of the investigation to be described here to determine the apparent RBE of the heavy particles thus liberated for acute effects in the mouse.

Although there are many well recognized objections to the use of the term RBE (1, 2), it remains a useful expression, provided its limitations and necessary qualifications are recognized. In the present study, the RBE of a given radiation is taken as the ratio of the physically measured dose in rep of a standard radiation (Co^{60} gamma, or in this report 250-kvp x-radiation) to produce a given biological endpoint, to the dose of the radiation in question, delivered over approximately the same time interval, required to produce the same biological effect.

The RBE of different radiations has recently been reviewed (1, 2, 3), and the difficulties of obtaining meaningful values in the mammal are well recognized. Extensive studies have been made in the mouse and, despite the differences and uncertainties incident to the varying technics employed, fair agreement has been obtained in recent investigations. (Wide discrepancies in the earlier literature may be due in large part to the inadequacies of the radiation sources then available.) The RBE of high-energy x-rays (200 or 250 kvp) for acute mortality and spleen-thymus weight loss in the mouse (1) is approximately 1.5 compared to Co^{60} gamma radiation. The RBE for fast neutrons, which liberate energy in tissues chiefly by means of the recoil protons from elastic collisions with the hydrogen in the tissue, have an RBE of between 1 and 3, and possibly higher. It appears likely that the figure may decrease as neutron energy increases over the range of approximately 1 to 20 MEV or higher. For thermal neutrons, which liberate energy in tissue largely through the recoil proton from nitrogen capture, the RBE has been reported to be between 1.5 and 2, compared to 250-kvp x-radiation.

Hollcroft and Lorenz (4) attempted to determine the RBE of alpha particles in the intact mouse by injecting radon in equilibrium with its decay products. Over 90 per cent of the total dose was con-

[1] From the Medical Department, Brookhaven National Laboratory, Upton, L. I., New York. This work was supported by the U. S. Atomic Energy Commission. Presented at the Forty-first Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 11–16, 1955.

sidered to have been delivered by the alpha particles from two decay products of radon, radium A and radium C′. The effectiveness of these particles relative to 186-kvp x-rays for thirty-day mortality in the mouse was found to be approximately 1. The authors point out, however, that the uneven distribution of the dose with radon in various organs made strict comparisons with x-radiation difficult. Basson and Shellabarger (5) obtained an RBE of approximately 3 for the alpha particles from astatine, compared to the beta particles from I^{132}, using thyroid function in the rat as the biological endpoint. It is difficult to compare these results directly with those of Lorenz, since the effectiveness of the I^{132} beta rays relative to x-rays is not known for the endpoint employed *i.e.*, thyroid function, and the distribution of beta dose in the rat thyroid is not uniform.

In the present studies, single whole-body doses of thermal neutron radiation were delivered to mice which had been injected previously with boron in the form of borax. The biological endpoint studied was the degree of spleen and thymus weight depression. The degree of effect produced by the recoil particles from boron capture was determined by subtracting the rem dose due to thermal neutrons alone from the total dose delivered.

MATERIALS AND METHODS

Irradiation Facilities: Mice were irradiated in the medical facility of the Brookhaven Research reactor, which has been previously described (6, 7). A general view of the facility and of the mouse exposure apparatus is shown in Figure 1. Leakage neutrons from the graphite reflector were funneled through the cone arrangement to the irradiation area. The cylindrical shield of bismuth metal was used to reduce further the amount of gamma radiation accompanying the neutrons. Although the flux varied with changing reactor power level and reactor control rod pattern, the average flux with all mice in place was approximately 1.5×10^9 n/cm.^{2}-sec. with the reactor operating at 24 megawatts. All exposures were less than twenty-five minutes in duration. The time required to open and close the shutter was taken into account

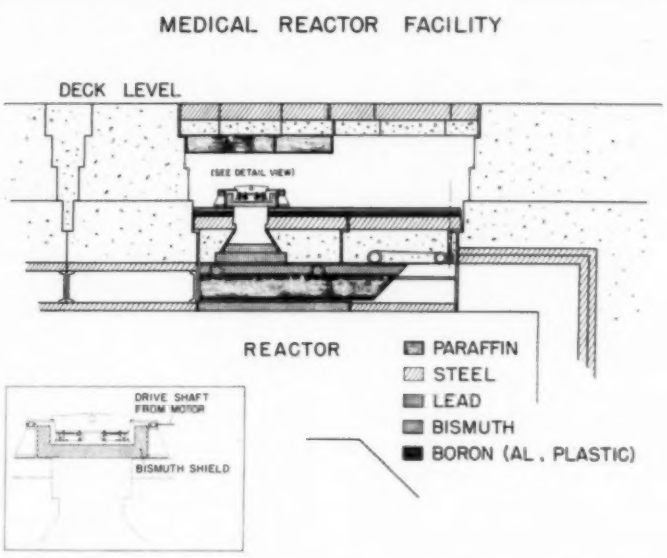

Fig. 1. Medical facility of the Brookhaven research reactor, showing the method of animal exposure.

in determining the *nvt* (integrated flux, or total neutrons/sq. cm.). The thermal neutron beam was calibrated against the Brookhaven Sigma Pile with the use of gold foil activation data. This calibration agreed within 10 per cent with that obtained from calculations based on sodium activation data and the published cross section for sodium. Intercalibration using gold foils was also obtained with Messrs. E. Tochilin and B. Shumway of the U.S.N. Radiological Defense Laboratory in San Francisco, and readings were within 8 per cent agreement. Similar intercalibration with Drs. Wright, Langham, and Payne Harris of the Los Alamos Scientific Laboratory indicated agreement within 2 per cent. Covering the gold foils with 1 mm. of cadmium reduced the reading to approximately 1 per cent of its value, indicating that the error in flux measurements resulting from the gold resonance peak at 4 ev was negligible.

For the determination of dose rates due to thermal neutrons alone, it was necessary to obtain estimates of the dose from the inherent 4-MEV gamma rays from the reactor graphite and from the 2.2-MEV gamma radiation resulting from capture of thermal neutrons in hydrogen in the Lucite exposure apparatus and in the exposed animals themselves. The gamma component was determined by three methods: (*a*) The graphite carbon-dioxide-gas-flow chamber described by Handloser and Oleson (8) was exposed in the thermal neutron beam, with and without exposure apparatus and animals. (*b*) Chemical dosimeters[2] and a Landsverk ionization chamber were enclosed in sufficient metallic lithium to reduce the thermal neutron flux to negligible levels. This procedure is similar to the one described by Brennan *et al.* (9). (*c*) In addition, nitrogen-free "tissue-equivalent" chambers designed by Dr. H. H. Rossi were exposed in the reactor beam. The agreement obtained with the three methods was good and the total gamma contamination (inherent, inter-mouse, and Lucite contributions) was found to be 300 r/hr. at a flux of 1.47×10^9 n/cm.^{2}-sec. Of the 300 r/hr. total gamma radiation, 220 r/hr. were accounted for by the intrinsic reactor radiation, 30 r/hr. were from hydrogen capture in the Lucite exposure apparatus, and 50 r/hr. represented inter-mouse gamma rays from hydrogen capture in tissue. Thus 1 r of intrinsic radiation is obtained with each 2.40×10^{10} nvt, and 1 r of 2.2-MEV gamma radiation is obtained with each 6.63×10^{10} nvt.

Mice were also exposed to gamma radiation in a cobalt-60 irradiator maintained in the Brookhaven Medical Department. The animals were held, 30 at each irradiation, in a Lucite box, $25 \times 25 \times 4$ cm., placed 12 inches above a cobalt source. This source consisted of 21 slugs of cobalt 60 arranged so as to give an essentially uniform field of exposure. A stream of air supplied for ventilation during irradiation kept the mice in motion and increased the uniformity of dosage to the group. The dose rate was approximately 8 r/min.

Irradiation Procedures: Mice were transported by automobile from the animal holding quarters to the Brookhaven reactor for thermal neutron irradiation. Since two days were required for the exposure, the experiment was performed in replicate and the data were combined. Ten mice were placed, unanesthetized, in Lusteroid centrifuge cones and positioned radially on the lower side of a Lucite disk (Fig. 1). The 0.35-mm.-thick plastic thus interposed between the mice and the neutron beam was found not to produce any measurable effect on the neutron flux. At each exposure, two groups of 3 mice receiving the two doses of boron employed, and one group of 3 mice receiving glucose only, were irradiated simultaneously. The single exception to this procedure will be apparent in the data presented below. Except in the event of mechanical failure, the mouse holder was rotated during exposure to minimize the effect of possible inhomogeneities in the beam. Each ex-

[2] The authors are indebted to Lt. S. C. Sigoloff, U.S. Air Force, for performing this calibration.

posure was monitored with a gold foil attached to the circulating disk, and this reading was used in calculating the nvt for that exposure. This procedure was necessary, since the flux varied with changing control rod pattern and could not be determined with sufficient accuracy from previous foil readings and reactor power level alone.

In a separate series of exposures, the possibility of a "sink" effect (9) from neutron capture in the mouse tissues was explored by successively adding mice to the exposure wheel and examining the effect on the readings of gold foils placed on the proximal surface of the initial mouse. No detectable change in flux value was obtained by the addition of the animals, indicating the absence of a significant "sink" effect under the exposure geometry employed.

Animals; Biological Procedures: Female CF1 mice, obtained at three to four weeks of age from Carworth Farms, were used at the age of five to seven weeks. All were maintained in air-conditioned rooms and were given food and water *ad libitum*. The animals were divided into groups of approximately equal weight distribution. "Stressed control" groups were subjected to all experimental procedures, including transportation to the reactor and confinement in the Lusteroid cones, except the actual irradiation.

Spleen-thymus weight determinations were made essentially as previously described (10). In an initial serial-sacrifice experiment, it was found that minimum weight values occurred on the third and fourth post-exposure days for both cobalt-60 and reactor radiations except at very low doses. Therefore, all animals were sacrificed at approximately three and one-half days, ether anesthesia being used for this purpose. The spleen was removed and weighed immediately. The thymus was removed and placed in Carnoy's solution for twenty-four hours. The fat and connective tissue were then dissected from the organ, and it was blotted dry and weighed. The thymus tissue fixed in Carnoy's solution was whiter than that fixed in formalin (11), and removal of fat and connective tissue was thus facilitated. Because of the volatility of Carnoy's fixative, rigid standardization of the blotting and weighing procedure was necessary. The spleen and thymus tissues were prepared for histological examination.

Boron; Initial Irradiation Exposure: Both natural boron and B^{10}-enriched boron obtained from the Atomic Energy Commission Laboratory at Oak Ridge were used in these studies. Natural boron contains 81 per cent of B^{11} (cross section of 4.5 millibarns for thermal neutrons) and 19 per cent of B^{10} (cross section of 4,010 barns; see reference 12). The enriched mixture consists approximately of 96 per cent B^{10} and 4 per cent B^{11}. All boron was administered in the form of borax, $Na_2B_4O_7.10H_2O$. Borax containing enriched boron was synthesized in the Brookhaven medical department. The borax was dissolved in a *d*-glucose solution in the ratio of 1 mole of borax to 2 moles of *d*-glucose. The toxicity of borax at higher dose levels (13) has been found to be diminished by glucose. Each animal received a volume of 0.01 ml./gram, resulting in a dose of 25 μg of boron per gram of tissue.

In an initial spleen-thymus weight study of 160 mice, an RBE of 1.4 for spleen weight loss and 1.7 for thymus weight loss was obtained, with Co^{60} radiation as the standard. The calculations of necessity involved subtraction of the effect of the reactor radiations alone from that of the reactor radiations and the recoil particles from boron capture. It was thus necessary to establish that the effects of the two types of radiation are completely additive. This was investigated by using two concentrations of B^{10}. To avoid the possibility of chemical effects resulting from different concentrations of borax influencing the results, solutions of identical borax and boron concentration but different B^{10} concentrations were obtained by adding B^{10}-enriched borax to ordinary borax. Mice receiving one of each of the two different boron-glucose solutions and mice

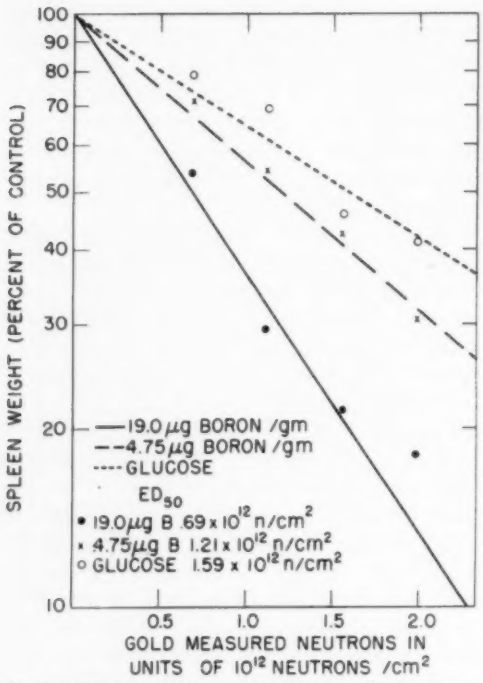

Fig. 2. Spleen weight as a function of gold-measured thermal neutron nvt.

receiving glucose alone in identical concentration were exposed to graded doses of thermal neutron radiation.

Depth-Flux Measurements: Gold foils were placed in the body of a sacrificed, semi-frozen mouse in such a way that minimum self-shielding would occur, and the flux as a function of depth in the exposed animal was measured. In addition, thin gold wires were inserted obliquely through the median sagittal plane of the body. Thus self-shielding occurring during irradiation was minimal. Following exposure, the wire was cut into small pieces, weighed, and counted. The flux, by both methods, was found to fall off in an approximately exponential fashion with a half-value layer of 2.4 cm. This compares with a half-value layer of 1.85 cm. obtained for larger tissue masses (14). The mid-line flux in the mouse was 73 per cent, and the exit flux was 53 per cent of the surface flux. The average flux to the mouse tissues, calculated from the depth-flux data by integrating the exponential function between the limits of 0 and 2.2 cm. (the measured average thickness of the mouse in the Lusteroid centrifuge tubes) and dividing the value obtained by the average mouse thickness, was found to be 75 per cent of the surface dose.

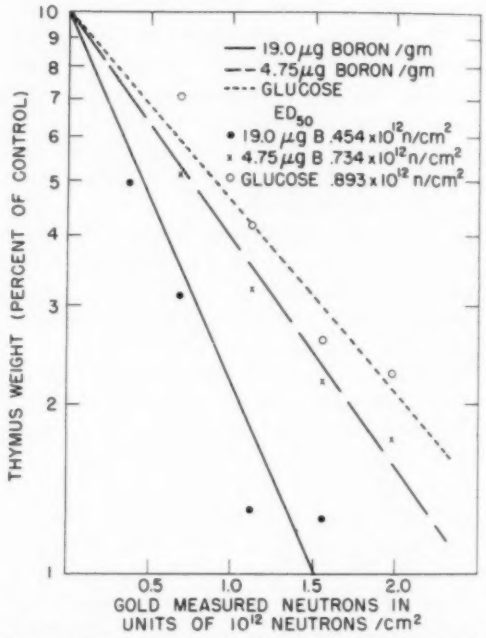

Fig. 3. Thymus weight as a function of gold-measured neutron nvt.

In subsequent calculations, the surface flux is used in calculating exposures and doses received by the mice.

Boron Distribution Studies: Since the dose from boron capture particles is a direct function of the concentration of boron in the tissues, the distribution of the element in the mouse was determined. A modification of the quinalizarin method described by MacDougall and Biggs (15) was used. The mice were injected with 50 μg of boron per gram of body weight and were sacrificed serially at five, ten, fifteen, twenty, and twenty-five minutes following injection. This was done by dropping them into a mixture of dry ice and acetone in order to preserve, so far as possible, the distribution of boron in the blood

TABLE I: SPLEEN AND THYMUS WEIGHTS FOLLOWING THERMAL NEUTRON IRRADIATION OF MICE INJECTED WITH BORON

Gold-measured neutrons/cm.^{2}	No. of mice	Spleen Weight mg.	Spleen Weight Per cent of control	Thymus Weight mg.	Thymus Weight Per cent of control
	19.0 micrograms B^{10}/gram mouse; Neutron irradiation				
0.367×10^{12}	9	66.6	68.7	27.8	49.6
0.679×10^{12}	18	52.5	54.1	17.5	31.2
1.120×10^{12}	18	28.6	29.5	7.3	13.0
1.545×10^{12}	14*	20.8	21.4	7.0	12.5
1.965×10^{12}	4*	17.5	18.0	5.3	9.5
	4.75 micrograms B^{10}/gram mouse; Neutron irradiation				
0.679×10^{12}	18	69.7	71.9	28.6	51.1
1.120×10^{12}	18	52.8	54.4	17.9	32.0
1.545×10^{12}	18	41.4	42.7	12.3	22.0
1.965×10^{12}	18	29.6	30.6	9.7	17.3
	Glucose only; Neutron irradiation				
0.679×10^{12}	18	77.5	79.9	39.7	70.9
1.120×10^{12}	18	68.0	70.1	23.3	41.6
1.545×10^{12}	18	44.8	46.2	14.6	26.1
1.965×10^{12}	18	40.5	41.8	12.8	22.8
	Stressed controls				
0.0	36	97.0	100.0	56.0	100.0

* Animals died prior to sacrifice time.

TABLE II: SPLEEN AND THYMUS WEIGHT LOSS FOLLOWING COBALT-60 GAMMA IRRADIATION

Dose (r)	No. of Animals	Boron Injected	Spleen Weight mg.	Spleen Weight Per cent of control	Thymus Weight mg.	Thymus Weight Per cent of control
200	30	Yes	71.4 ± 6.3*		24.7 ± 2.1	
	30	No	70.4 ± 6.3		27.8 ± 2.7	
	60	Combined	70.9 ± 4.4	68.1	26.3 ± 1.7	49.0
400	30	Yes	46.2 ± 4.7		15.2 ± 1.2	
	30	No	45.5 ± 4.5		16.1 ± 1.6	
	60	Combined	45.9 ± 3.2	44.1	15.7 ± 1.0	29.2
600	30	Yes	36.4 ± 3.2		13.2 ± 0.9	
	30	No	38.1 ± 2.5		12.1 ± 1.4	
	60	Combined	37.3 ± 0.7	35.8	12.7 ± 0.8	23.6
0	30	Yes	101.1 ± 9.7		56.7 ± 5.6	
(Control)	30	No	107.1 ± 10.3		50.7 ± 4.7	
	60	Combined	104.1 ± 7.0	100.0	53.7 ± 3.6	100.0

* Standard error of mean.

and tissues at the time of sacrifice. Tissues were then removed and digested in a papain mixture for a period of forty-eight hours. Following complete digestion, they were read against standard curves prepared for each. It was not possible to obtain sufficient bone marrow from the mouse for concentration studies. Therefore, since the bone marrow is known to be of major importance in radiation damage to the mammal (1), the concentration in that tissue was determined in rats given the same dose of boron per unit of body weight as were the mice. The contents of the small intestine were removed but the organ was not washed, as washing was found to lower the boron content.

RESULTS

Spleen-thymus weight loss data for neutron and boron capture irradiation are summarized in Table I, and the regression of organ weight loss on neutron exposure is shown in Figures 2 and 3. The effects of Co^{60} irradiation on spleen and thymus weight are given in Table II and Figure 4. All regression lines were fitted by the method of least squares.

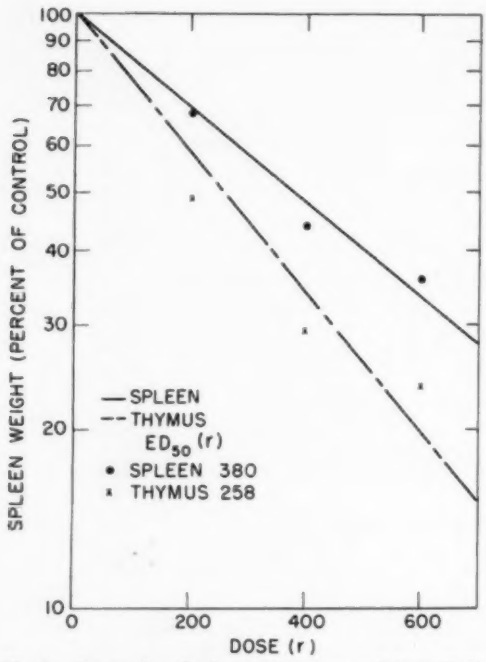

Fig. 4. Regression of spleen and thymus weight on Co^{60} gamma radiation dose.

Although the results can be analyzed by comparing the slopes of the regression lines, it was considered more convenient to compare the radiation exposure necessary to produce the same degree of effect. The exposures required for reduction of the organ weights to 50 per cent of the control value were compared; this end-point was termed the ED_{50}. The ED_{50} for Co^{60} gamma radiation was 380 r for the spleen and 250 r for the thymus. Corresponding values for 250-kvp x-radiation,[3] taken from a previous report (9), are 258 r for the spleen and 180 r for the thymus. The effectiveness of the x-radiation employed, relative to Co^{60} gamma radiation for these end points, is thus approximately 1.5. The calculated ED_{50} values for animals exposed to thermal neutrons are shown in Table IV.

From Table II it can be seen that boron injected prior to gamma irradiation did not alter the effect of this radiation on the spleen and thymus weight. Thus, the effects noted with thermal neutron irradiation after boron injection can be assumed to be due to boron capture only and not to possible chemical action of the drug.

Histologic examination[4] of the spleen and thymus revealed typical radiation effects, which were commensurate in degree with the dose received. No qualitative differences in effects could be attributed to boron capture or to the drug administered.

RBE of Thermal Neutrons Alone: The RBE of the thermal neutrons is the dose at the ED_{50} point delivered to the glucose-injected control mice by the thermal neutrons alone, divided by the rep dose. However, the total rem dose observed at the ED_{50} point for the spleen, 380 rem, was delivered not only by the thermal neutrons, but by the intrinsic 4-MEV gamma radiation of the reactor and by the 2.2-MEV gamma radiation from hydrogen capture in the Lucite exposure apparatus and in tissues as well. The intrinsic gamma radiation was shown earlier in the report to be approximately 1 r for each 2.40×10^{10} nvt, or 66 at the spleen ED_{50} point. This highly energetic radiation is less effective than 250-kvp x-radiation or lower-energy gamma radiation (9, 16); its effectiveness relative to Co^{60} gamma radiation is taken as 0.90, and relative to 250-kvp x-radiation, as 0.6. Thus the 66 r of measured reactor gamma radiation becomes 59 rem of Co^{60} gamma radiation. The gamma dose from the exposure apparatus and the mice was shown to be 1 r for each 6.63×10^{10} nvt, or 24 r at the ED_{50} point. The effectiveness of this radiation was taken as unity relative to Co^{60} gamma radiation, and as 0.7 relative to 250-kvp x-radiation. The total rem dose at the ED_{50} point due to thermal neu-

[3] These data were obtained on CF1 mice sacrificed on the fifth post-exposure day. More recent but less complete data on CF1 mice sacrificed three and one-half days after exposure are, however, in substantial agreement (ED_{50} of 240 r for the spleen; 200 r for the thymus).

[4] The authors are indebted to Dr. E. P. Cronkite, of the Brookhaven National Laboratory, and to Dr. George Brecher, of the National Institutes of Health, Bethesda, Md., for interpreting the histologic sections.

TABLE III: CALCULATION OF RBE FOR THERMAL NEUTRONS

	Spleen Weight Loss End Point		Thymus Weight Loss End Point	
	Compared to Co^{60} gamma standard	Compared to 250-kvp X-ray standard	Compared to Co^{60} gamma standard	Compared to 250-kvp X-ray standard
ED_{50} in rem	380	250	258	180
ED_{50} for thermal neutrons/cm.^{2}	1.59×10^{12}	1.59×10^{12}	0.893×10^{12}	0.893×10^{12}
Intrinsic gamma radiation from the reactor, at ED_{50}	66 r; 59 rem	66 r; 40 rem	37 r; 33 rem	37 r; 22 rem
Inter-mouse and Lucite gamma dose	24 r; 24 rem	24 r; 17 rem	13 r; 13 rem	13 r; 9 rem
Rem dose at ED_{50} due to thermal neutrons alone	297 rem	193 rem	212 rem	149 rem
nvt of thermal neutrons equivalent to 1 rem	0.54×10^{10}	0.82×10^{10}	0.42×10^{10}	0.60×10^{10}
Dose at ED_{50} from hydrogen capture gammas	28.8 rep	28.8 rep	16.2 rep	16.2 rep
Dose at ED_{50} from protons from nitrogen capture	49.0 rep	49.0 rep	27.5 rep	27.5 rep
Total rep dose at ED_{50} due to thermal neutrons alone	77.8 rep	77.8 rep	43.7 rep	43.7 rep
RBE of thermal neutrons; rem/rep	3.8	2.5	4.9	3.4
RBE of 0.62 MEV protons from nitrogen capture	5.5	3.4	7.1	4.8

trons alone is thus $380 - (59 + 24) = 297$ rem of Co^{60} gamma radiation. The results of similar calculations for the thymus, and for the spleen and thymus, with 250-kvp x-radiation (Westinghouse) instead of Co^{60} gamma as the standard are shown in Table III.

The biological effectiveness of thermal neutrons was calculated from these values, with the results given in Table III. For spleen weight loss, approximately 0.5×10^{10} nvt of thermal neutrons were found to be equivalent in effect to 1 rem of Co^{60} gamma radiation, and approximately 0.8×10^{10} were found equivalent to 1 rem of 250-kvp x-radiation.

The total rep dose from thermal neutrons alone was calculated from their known interactions with tissue. Essentially all of the energy released in tissue is derived from the 0.62-MEV recoil protons from nitrogen and from the 2.2-MEV gamma ray from hydrogen capture (the dose contribution from induced radioactivity in the tissues is negligible). The dose in rep at the ED_{50} level for a given neutron-capturing element in the tissues was obtained by means of the following equation (the mouse was assumed to be a "thin foil" and only first collisions were considered):

$$\text{rep}/ED_{50} = (nvt)\,(N)\,(\sigma_c)\,(E)\,(1.71 \times 10^{-8})\,(A) \quad (1)$$

where

nvt = integrated flux or neutrons/sq. cm. at the ED_{50} value
N = number of atoms of the element per gram of tissue
σ_c = capture cross section for thermal neutrons for the element
E = energy of the radiation(s) emitted by the element, in MEV
A = the fraction of the liberated energy absorbed in the body

The factor 1.71×10^{-8} converts MEV/gram to rep, using 93 ergs/gram as 1 rep.

For protons or heavier particles, $A = 1$. The value for A in the mouse for the 2.2-MEV gamma liberated in the hydrogen-capture process has been calculated by Brennan (9). The value obtained for a 21-gram mouse was 0.025. The percentages of hydrogen and of nitrogen in the tissues are taken as 10.0 and 4.0 per cent, respectively.

The rep dose at the ED_{50} value for spleen weight loss is:

For hydrogen,

$$(1.59 \times 10^{12})\,(6.02 \times 10^{22})\,(0.32 \times 10^{-24})\,(2.2)\,(1.71 \times 10^{-8})\,(0.025) = 28.8 \text{ rep}$$

For nitrogen,

$$(1.59 \times 10^{12})\,(1.71 \times 10^{21})\,(1.7 \times 10^{-24})\,(0.62)\,(1.71 \times 10^{-8}) = 49.0 \text{ rep}$$

The total rep dose is thus 77.8 rep.

Values for the RBE of thermal neutrons (rem/rep), determined from the above

TABLE IV: CALCULATION OF RBE OF HEAVY PARTICLES FROM BORON CAPTURE

	Spleen Weight Loss End Point						Thymus Weight Loss End Point					
	Compared to Co^{60} gamma standard			Compared to 250-kvp X-ray standard			Compared to Co^{60} gamma standard			Compared to 250-kvp X-ray standard		
	G*	B_1*	B_2*	G	B_1	B_2	G	B_1	B_2	G	B_1	B_2
ED_{50} in rem	380	380	380	250	250	250	258	258	258	180	180	180
ED_{50}, thermal neutrons (units of 10^{12} nvt)	1.59	1.21	0.69	1.59	1.21	0.69	0.893	0.734	0.454	0.893	0.734	0.454
Total rem/nvt (units of 10^{12})	239	314	551	157	206	362	289	352	569	202	246	397
rem/nvt due to B^{10} alone (units of 10^{12})	...	75	312	...	49	205	...	63	280	...	44	195
Relative rem doses	...	1	4.2	...	1	4.2	...	1	4.4	...	1	4.4
Relative B^{10} doses injected	...	1	4.0	...	1	4.0	...	1	4.0	...	1	4.0
rep/nvt due to B^{10} only (units of 10^{12})												
using $\alpha + Li^7$ nuclei	...	46	184	...	46	184	...	46	184	...	46	184
using α only	...	29	116	...	29	116	...	29	116	...	29	116
RBE of heavy particles												
using $\alpha + Li$ nuclei	...	1.63	1.70	...	1.06	1.11	...	1.37	1.52	...	0.96	1.06
using α only	...	2.59	2.70	...	1.69	1.76	...	2.17	2.41	...	1.53	1.69

* Letters refer to thermal neutron exposure with injected glucose only (G), injected boron 4.75 μg B^{10}/gram (B_1) and injected boron 19.0 μg B^{10}/gram (B_2).

calculations, are shown in Table III. It is seen that the RBE determined for spleen and thymus weight loss was approximately 3.8 compared to Co^{60} gamma radiation, and 2.5 compared to 250-kvp x-radiation.

The RBE of the recoil protons from nitrogen capture was also calculated, as follows: If the effects of gamma and proton radiation are assumed to be completely additive, and if the effectiveness of the 2.2-MEV gamma radiation from hydrogen is taken as unity compared to Co^{60} gamma rays, the rem dose at the ED_{50} due to proton radiation alone (spleen weight loss) is (297 − 28.8) or 268 rem. The corresponding rep dose is 49 rep, and the RBE of the recoil protons is the ratio of the two. The values obtained (Table III) are approximately 5.5 compared to Co^{60} gamma radiation, and 3.4 compared to 250-kvp x-radiation.

Rem Dose Rates from Boron Capture: The rem dose rates (rem/10^{12} nvt) were determined from ED_{50} values obtained from the regression lines (Figs. 2, 3, and 4, and reference 9), with the results shown in Table IV. The rem dose rates resulting solely from boron capture in the boron-injected animals were obtained by subtracting the rem dose due to the reactor radiations alone (the glucose-injected control animals) from that due to both boron capture and the reactor radiations. Both of the concentrations of boron used markedly altered the dose rate. The 4.75 μg B^{10}/gram concentration of boron was sufficient to raise the rem dose rate by a factor of approximately 1.25, and a factor of approximately 2.1 was obtained with the 19.0 μg B^{10}/gram concentration.

It should be noted that the ratios of rem doses due to boron alone, for the two concentrations of drug used, are 4.2 for spleen weight loss and 4.4 for thymus weight loss. These values are not significantly different from the ratio of boron concentrations used, 4.0, indicating the complete additivity of the radiation from boron capture and from slow neutron irradiation alone. The validity of obtaining the dose due to boron capture alone by subtracting that due to reactor radiations alone is thus established.

Calculations of rep from Boron Capture; RBE of the Heavy Particles: The calculation of the RBE of the recoil particles from boron capture does not depend upon the calculation of rep from thermal neutrons alone. This is true since the demonstration of complete additivity of radiations from boron capture and those from the reactor makes it possible to subtract as a unit the rem dose due to all reactor radiations. The rep dose corresponding to the remaining rem dose due to boron capture can then be calculated, and the RBE of the heavy recoil particles determined.

The injected boron was assumed to be uniformly distributed throughout the body, at the average concentration administered, for the duration of exposure to thermal neutrons. The actual concentrations, as determined experimentally, are shown in Table V.

The rep doses from boron capture were calculated from Formula 1 (above). The nvt values at the ED_{50} points and the rem dose rates are given in Table IV. The values to be used for N, σ_c, and A require no elaboration; the value to be used for E, however, requires further consideration.

The energetics of the B^{10} (n, α)Li^7 reaction have been considered by Rhodes *et al.* (17). The total energy released in the reaction, or Q value, is 2.793 MEV, of which 0.479 MEV is dissipated as gamma emission in 94.1 per cent of disintegrations. The dose from this source to a mouse injected with boron, and the dose from simultaneously exposed mice receiving boron, was calculated by essentially the same method as that employed by Brennan (9). The total dose received from this source, for the highest concentration of boron used and for the longest exposure time, was calculated to be less than 1 r. It was accordingly disregarded in the subsequent calculations.

After subtraction of the gamma-ray energy, there remain 2.314 MEV, dissipated as an 1.473-MEV alpha ray and a

TABLE V: DISTRIBUTION OF BORON IN MOUSE TISSUES FOLLOWING THE INTRAVENOUS INJECTION OF 50 μg./GRAM OF BORON IN THE FORM OF BORAX

Tissue	Boron Concentration, μg/gram Tissue*				
	5 min.†	10 min.	15 min.	20 min.	25 min.
Spleen	56 ± 6‡	48 ± 10	57 ± 10	45 ± 10	54 ± 11
Thymus	34 ± 8	38 ± 9	24 ± 5	35 ± 8	20 ± 8
Liver	55 ± 11	71 ± 19	47 ± 8	52 ± 14	54 ± 12
Small bowel	46.2 ± 23	49.2 ± 18	57.5 ± 24	47.0 ± 19	47.3 ± 17
Muscle	68 ± 8	76 ± 14	76 ± 11	60 ± 11	73 ± 17
Kidney	76.9 ± 26	62.4 ± 28	63.5 ± 27	65.2 ± 31	55.5 ± 25
Heart	51.7 ± 16	45.8 ± 18	40.5 ± 19	38.8 ± 18	38.5 ± 20
Lung	44.2 ± 16	50.4 ± 20	45.6 ± 21	40.2 ± 25	44.2 ± 20
Bone marrow§	62.4 ± 28	43.0 ± 24	43.2 ± 28	53.0 ± 29	50.5 ± 27
Blood	47.8 ± 0.49	46.4 ± 0.82	42.0 ± 0.99		35.4 ± 1.2**

* Average of values from 10 mice.
† Time from boron injection to sacrifice.
‡ Standard deviation.
§ Rat marrow, 5 to 7 animals per point.
** Thirty-minute sample.

0.841-MEV Li particle. Thus, the total energy dissipated as heavy-particle radiation is 2.314 MEV in 94.1 per cent of all emissions, and 2.793 MEV in 5.9 per cent of emissions. The weighted mean value of 2.34 MEV was used in the rep calculation.

The rep dose rate (rep/10^{12} thermal neutrons) for spleen weight loss, using the 4.75 μg B^{10}/gram concentration of boron, was calculated as follows (see Equation 1):

$$(1.0 \times 10^{12})\ (2.86 \times 10^{17})\ (4010 \times 10^{-24})\ (2.34)\ (1.71 \times 10^{-8})\ (1) - 46 \text{ rep}/10^{12} \text{ nvt}$$

The resulting RBE for the heavy particles, rem/rep, is accordingly 75/46 or 1.63. If only the alpha particle is considered in the calculation, the rep dose rate becomes 29 rep/10^{12} nvt, and the RBE becomes 2.59.

Corresponding values for thymus weight loss, and for comparison with 250-kvp x-radiation, are shown in Table IV. The average value for the RBE, for both spleen and thymus weight loss, using the energy of both the recoil α and Li particles in the calculation, was 1.56 as compared with Co^{60} radiation and 1.05 compared to 250-kvp x-radiation. The corresponding values, if only the α-particle is considered, were 2.47 and 1.67, respectively.

It is apparent that the figure reported for the RBE of the heavy particles from boron capture of thermal neutrons depends on the particular values chosen for the several parameters entering into its calculation. Thus, if the mid-line flux rather than the entrance flux is used in the determinations, the RBE is increased by a factor of 1.4. Use of the average boron dose found to exist in the spleen (Table V), instead of the average dose used for the body as a whole, would not appreciably alter the RBE. The average concentration in the thymus was less than that for the entire body. Using the value obtained by organ analysis for boron would increase the RBE, yielding a value closer to that obtained for the spleen.

DISCUSSION

The value of approximately 0.8×10^{10} thermal neutrons per square centimeter, found in the present study to be equivalent in effect to 1 r of 250-kvp x-radiation, is in good agreement with the value of 0.79×10^{10} reported by Lewis (18) at Brookhaven Laboratory, using weight loss in the rat as the biological endpoint, and with the value of 0.82×10^{10} reported by the Los Alamos group (16) for testicular atrophy in the mouse. It is at variance, however, with the value of approximately 1.3×10^{10} reported by the Los Alamos group for spleen-thymus weight loss and acute mortality in the mouse (16), and with the value of 1.7×10^{10} reported by Upton *et al.* (19) at Oak Ridge National Laboratory, for acute lethality in mice. These differences appear to be larger than

might be expected from biological variations alone. Some difference might be anticipated on the basis of the geometry of exposure, the thermal neutron flux being essentially isotropic under the conditions of exposure at the Los Alamos Laboratory and semicollimated under the conditions of the present study. Geometry in itself, however, probably would not explain the discrepancies. The excellent agreement with the Los Alamos Scientific Laboratory on intercalibration of flux would rule out this consideration as being responsible for the difference.

The RBE of thermal neutrons obtained (approximately 2.5 as compared with 250-kvp x-rays) is also higher than the value of approximately 1.5 to 1.7 obtained by the Los Alamos group (9, 16) for acute mortality and spleen-thymus weight loss in the mouse. This follows, of course, principally from the differences in the roentgen/nvt values which have been noted above.

The RBE value of 1.05 for the heavy recoil particles from boron capture (compared to 250-kvp x-rays) is in good agreement with the value of 1 reported by Hollcroft and Lorenz (4) for alpha-particle irradiation derived from radon injected into mice, with acute mortality as the endpoint. It is considerably lower, however, than the values of 20 or more reported for alpha irradiation of microorganisms (2). It is appreciably less, also, than the RBE obtained by the Los Alamos group (9, 16) and, in the present study, for thermal neutrons or recoil protons from nitrogen capture only. And since all of the RBE values of the present study were calculated from data on mice simultaneously exposed, it would appear reasonably certain that the relative values, if not the absolute values, are correct. This would lend support to the suggestion that the RBE in the mouse may pass through a maximum as the linear energy transfer (LET) of the irradiating particles increases. This observation has been made on microorganisms, with the maximum RBE occurring at LET values obtained with alpha particles of several MEV energy (2, 20). It should be remembered that the recoil Li^7 nucleus is heavier than an α-particle and has a correspondingly higher LET.

The validity of including the energy from the recoil Li particle in the dosage calculations might be questioned on the grounds that its short range in tissue (approximately 4 μ) would decrease the effectiveness of the released energy. It has been found, however, that the extremely soft beta particles from tritium (0.018 MEV, range of approximately 2.3 μ in tissue) are biologically effective in the mammal, with an RBE of approximately 1.4 compared to x-radiation (21, 22). This would lend support to the inclusion of the short-range Li nucleus in the dosage calculation. Additional evidence is available from work in progress with neutron capture in Li^6, in which energetic alpha and tritium particles are liberated. The RBE for spleen-thymus weight loss with the use of this reaction is approximately the same as that obtained with the boron capture reaction when only the alpha particles from $boron^{10}$ are used in the calculation.

The spleen and thymus end-point was employed primarily because of its simplicity and the ease with which it yields quantitative biological data. It is an empirical procedure that allows accurate comparison of effects. It has been pointed out (23) that the method has some theoretical disadvantages, stemming chiefly from the fact that the spleen and thymus are affected not only by radiation absorbed in the organs themselves, but to some degree, also, from radiation absorbed in distant tissues (24). Thus, the endpoint is complex, as is mortality. The degree to which the indirect or "abscopal" effect alters the spleen or thymus with whole-body radiation is not known (25). With partial-body irradiation (24), significant abscopal effect on the thymus and spleen was obtained only if the animals were made obviously ill by the irradiation, as evidenced by lethargy and other signs.

That mice usually show no signs of illness at the ED_{50} dose level would indicate that with total-body irradiation at this level relatively little of the spleen-thymus weight depression may result from abscopal effects. Additional support for this thesis is seen in recent work on adrenalectomized animals (26).

Little is known regarding the cellular distribution of boron; presumably, however, it is distributed with body water. It is possible that an apparently low RBE could be the result, at least in part, of a failure of boron, and thus of the short-range particles, to reach loci where maximum biological damage would result. It would therefore appear that conclusions concerning the dependency of biological effect on direct hits on sensitive volumes, or on the total energy liberated regardless of precise location, are not warranted by the data. It is also pointed out that, because of marked dependency of RBE values on the biological endpoint employed (1), extrapolation of the present results to other biological systems must be undertaken with caution. In particular, it is emphasized that the data do not necessarily apply to other than acute or short-term effects.

SUMMARY

Single whole-body doses of thermal neutron radiation were delivered by the Brookhaven reactor to female CF1 mice injected intravenously five minutes previously with boron in the form of borax. The biological endpoint studied was the degree of spleen and thymus weight depression when the animals are sacrificed three-and-one-half days after exposure. The rem dose rates from slow neutron irradiation and from the heavy particles from slow neutron capture by boron (alpha particle and recoil lithium nucleus) were found to be completely additive. The average rep dose from thermal neutrons alone and from boron capture was calculated, assuming the mouse to be a "thin foil," from the estimated tissue boron content, the slow neutron capture cross section for boron, the measured slow neutron flux at the proximal skin surface, and the energy release per neutron capture. The effectiveness of thermal neutrons alone, relative to Co^{60} gamma radiation (apparent RBE) was calculated to be 3.8. The apparent RBE of the heavy particles from slow neutron capture by boron was found to be approximately 1.6. This value was increased to 2.5 if the energy liberated by the alpha particle only was considered in the rep determination.

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Medical Department
Brookhaven National Laboratory
Upton, L. I., N. Y.

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SUMARIO

La Relativa Eficacia Biológica de los Neutrones Térmicos y de las Partículas Pesadas Derivadas de la Reacción del $B^{10}(n,\alpha)$ y el Li^7 para Efectos Agudos en el Ratón

Dosis únicas a todo el cuerpo, de radiación de neutrones térmicos fueron entregadas por el reactor nuclear del Laboratorio Nacional de Brookhaven a ratonas a las que se había inyectado intravenosamente cinco minutos antes boro en forma de bórax. El punto terminal biológico estudiado fué el grado de depresión del peso del bazo y del timo al sacrificar a los animales $3^1/_2$ días después de la exposición. Las tasas de dosis *rem* derivadas de la irradiación con neutrones lentos y de las partículas pesadas derivadas de la captura de neutrones lentos por el boro (partícula alfa y núcleo de reculada del litio) resultaron ser absolutamente aditivas. La dosis *rep* media derivada de los neutrones térmicos solos y de la captura de boro se calculó por el contenido de boro estimado en los tejidos, el corte cruzado de captura de neutrones lentos para el boro, el flujo medido de neutrones lentos en la superficie cutánea proximal y la liberación de energía por captura de neutrones.

La eficacia de los neutrones térmicos solos, en relación con la radiación gamma del Co^{60} (REB aparente), se calculó en 3.8. La REB aparente de las partículas pesadas derivadas de la captura de neutrones lentos por el boro resultó ser aproximadamente de 1.6. Este valor aumentaba a 2.5 si, en la determinación de la *rep*, sólo se consideraba la energía liberada por la partícula alfa.

DISCUSSION

Milton Friedman, M.D. (New York, N. Y.): I would like to ask the speaker to interpret for the radiotherapist the relative biological effectiveness in terms of qualities with which we are familiar? He gives a figure of 380 for Co^{60}, which isn't clear to me. And 2.34 MEV?

Dr. Bond: I think the difficulty lies in attempting to define a standard radiation to which we can compare radiations of unknown relative effectiveness. Radium gamma rays, cobalt-60 gamma rays, and x-rays of various peak energies and filtrations have been used as "standards," and it turns out that these radiations are not equally effective for many biological end-points. (Some of the apparent differences may be ascribed to dosimetric difficulties.) Thus, in general, 2,000-kvp x-rays may be somewhat less effective than 250-kvp; cobalt-60 or radium gamma rays still less effective. The value of 380 referred to is the dose of cobalt-60 gamma radiation required to reduce the mouse spleen weight by one half in our laboratory; only 250 r of 250-kvp x-radiation is required to accomplish the same end. The 2.34 MEV is the total energy liberated by the boron-capture reaction particles, the unknown radiations we attempted to

evaluate in our report. The use of standard radiations with differing relative effectiveness has resulted in considerable confusion in the study of RBE.

Harald H. Rossi, Ph.D. (New York, N. Y.): I would like to ask one question. Dr. Bond based his doses, I gathered, on a reading obtained by gold foils at the site of exposure. What was the dose distribution and flux distribution in the mouse?

Dr. Bond: We did depth flux measurements by inserting gold foils, and also gold wire, through the mouse. The results agreed well. The flux (and thus the dose very closely) fell off exponentially, as might be expected. The mid-line flux was about 75 and the exit flux about 50 per cent of the entrance flux. There was apparently a small amount of build-up at the entrance surface; however, we could not determine the amount accurately. The doses reported are the entrance doses.

Gioacchino Failla, Sc.D. (New York, N. Y.): I think there is some misunderstanding about the RBE of 10 for neutrons that has been used especially for protection purposes. This figure, applied to mammals, has never been established experimentally. Take, for instance, the value that Dr. Evans obtained with irradiated mice[1] during the war. There the ratio of doses as measured by the Victoreen chamber was about 8 for acute exposure and a similar figure was applied to chronic exposures. If one calculates what the RBE would be under those circumstances, it depends on what value is used to change from the n unit of the Victoreen chamber to the reading obtained with the tissue-equivalent chamber. Be that as it may, whether this factor be 2.5 or 5.5, you will never will get an RBE of 10 under those circumstances. It is closer to 4, or less. And this is the experience that most people have had in determining the RBE for fast neutrons with mammals.

The factor of 10 was used as a safe value for protection purposes, not because it had been obtained but because it seemed to be a fair value on the safe side. High values have been obtained for the RBE only in connection with the cataract problem, and there one may have an RBE of something like 10. Some people looking at Evans' results, which involved only a few mammals, even suggested that the RBE for cataract formation might be as high as 40, and so they went a little wild and wanted to have such a high RBE used for protection purposes. Actually, the experimentally determined values of RBE have been less than 10, except perhaps in the case of cataracts, so that these later experiments indicating a RBE much lower than 10 are not in conflict. I also have a feeling that the tendency is to make the RBE come out as low as possible and that, when things are ironed out in the next five years or so, it will be found that the true value is between what is being reported by some groups today and what was reported by other groups earlier in the game. So I think we should not speak of a "great difference" in RBE as we thought it was and as it is now being found to be.

[1] See Radiology **50:** 811–833, June 1948.

Relative Biological Effectiveness of Internal Emitters[1]

MIRIAM P. FINKEL, Ph.D.

PERMISSIBLE levels of exposure to radioactive materials have been based in large part upon two sets of comparisons. In the first, the radiotoxic hazards of the various isotopes are evaluated relative to radium in experimental animals. In the second, extrapolations are made to man through radium as the common link, since the latent effects of that element are known from individuals who have carried small but measurable body burdens for many years. In this work the mouse has proved to be a very useful experimental animal, particularly when relatively large populations are required. The data accumulated in such studies make possible an evaluation of the relative biological effectiveness (RBE) of different radioisotopes according to a number of criteria.

The effects of several alpha-emitters upon survival and upon the incidence of malignant bone tumors in mice have been reported previously (1). Subsequent experiments with several beta-emitters have now progressed to the point where preliminary comparisons can be made of a variety of radioisotopes with diverse physical properties. Since many animals in these studies are still alive (primarily in the groups that received moderate and low doses of Sr^{90}, Y^{90}, and Ca^{45}), and since many of the experiments are still awaiting final evaluation, only those comparisons based on acute lethality can be considered to be definitive at this time. Comparisons of crude mortality rates and of mortality rates with lymphoid tumors and with bone tumors serve only as indications of trends and as approximations of RBE. It is expected that the final analyses of the completed experiments will permit the extension of the comparisons in the direction of minimally effective and indifference doses, which is an area of major importance in establishing maximum permissible body burdens.

TABLE I: MATERIALS AND RANGE OF DOSES

Isotope	Range of Doses (μc/gm.)	No. of Dose Levels	No. of Mice
Ra^{226}	4.170 –0.0006	14	675
Pu^{239}	0.0504–0.00004	12	765
Po^{210}	0.097 –0.00046	9	645
U^{233}	0.10 –0.001	10	675
U^{232}	0.001 –0.0001	3	135
Th^{228}	0.360 –0.0066	6	75
Ru^{106}*	8.94 –0.57	5	40
Sr^{90}	9.33 –0.001	12	810
Sr^{89}	7.8 –0.05	7	352
Y^{90}	28.9 –4.7	10	103
P^{32}	7.36 –0.01	8	401
Ca^{45}	49.6 –0.016	10	448
Controls			1130
Total			6254

* From the work of Walton and Brues (2).

METHODS

Standardization of procedure, which facilitates comparisons among experiments, has been achieved in our routine radioisotope-toxicity studies by utilizing CF1 female mice injected intravenously at approximately seventy days of age. The animals are housed in metal cages and are fed commercially prepared food pellets. At acutely lethal dosages they are permitted to live until natural death occurs; at subacute and low levels animals *in extremis* are killed with Nembutal. Each animal is inspected for gross evidence of disease, and tissues are prepared for microscopic study. A postmortem skeletal roentgenogram is taken of every mouse. These general rules apply to all the experiments listed in Table I with the exception of the Ru^{106} study, in which 100-day-old mice were used, and the Sr^{89} study, in which the material was injected intraperitoneally. Radiophosphorus was given as phosphate, and plutonium (Pu^{++++})

[1] From the Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Ill. Work performed under the auspices of the U. S. Atomic Energy Commission. Presented at the Forty-first Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 11–16, 1955.

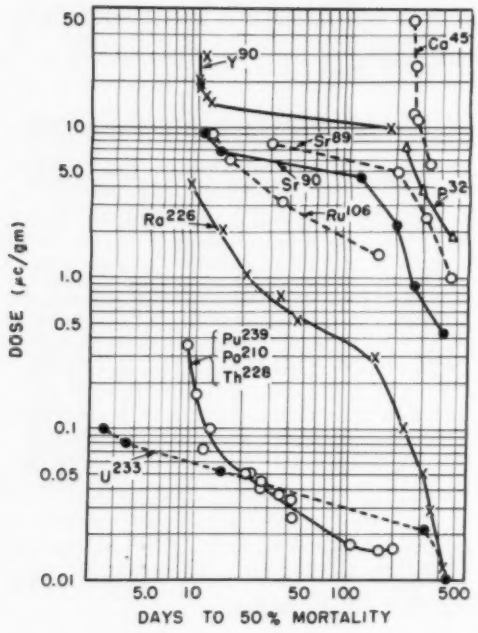

Fig. 1. Relationship between isotope dose and time to 50 per cent mortality.

and uranium as nitrates; all the other isotopes were injected as chlorides. The Ru^{106} solution contained 10 per cent Ru^{103}, the Sr^{89} solution contained less than 10 per cent Sr^{90}, and the Sr^{90} solution was an equilibrium mixture of Sr^{90} and Y^{90}.

RESULTS AND DISCUSSION

Time to 50 Per Cent Mortality: The acute lethality of irradiation, either from external sources or from internally deposited materials, is usually expressed as the LD 50/30 (or 20), which is the dose that kills 50 per cent of the exposed population in thirty (or twenty) days. For internal emitters, this value is most easily obtained by plotting on a log-log grid the number of days to 50 per cent mortality against the dose injected per unit weight. This method has the advantage of graphically presenting the LD 50 for any time interval that may be desired. Such a plot is presented in Figure 1, where a sharp separation is seen between the beta-emitters (Ca^{45}, P^{32}, Sr^{89}, Sr^{90}, Y^{90}, and Ru^{106}) and the alpha-emitters (Po^{210}, Th^{228}, Pu^{239}, and U^{233}); Ra^{226} occupies an intermediate position. Uranium was unique in that it killed very rapidly. None of the other isotopes, even in excessive doses, resulted in 50 per cent mortality in less than nine days. The acute lethality of high doses of U^{233} has been attributed to chemical toxicity, which may lead to death very

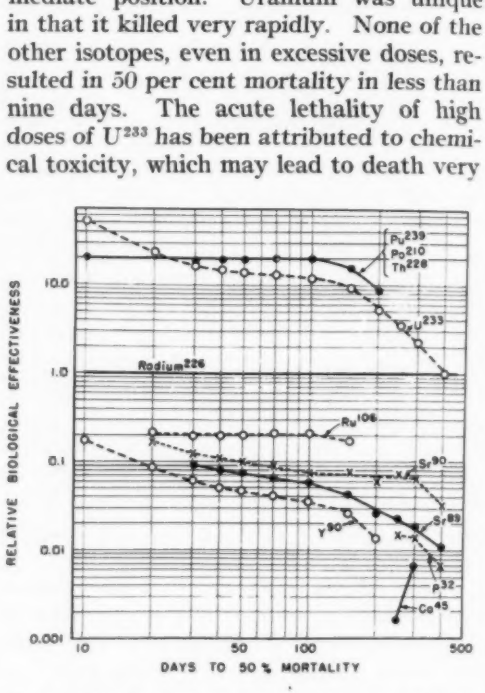

Fig. 2. Biological effectiveness relative to radium in killing 50 per cent of the population.

quickly, rather than to irradiation toxicity, which is manifested relatively slowly; 0.08 and 0.1 μc/gm., which were used here, exceed the chemically lethal dose of U^{233}, since these represent 8 and 10 μgm./gm., respectively (1, 3). Another deviation from the general pattern occurred in the case of Ca^{45}, which was no more effective as a lethal agent at a dose of 49.6 μc/gm. than it was at 11.2 μc/gm.

The relationships present in Figure 1 can be seen more readily in Figure 2, where the data have been plotted relative to radium, which has been given an arbitrary value of 1. In interpreting these results, one should remember that the abscissa, which represents increasing days to 50 per cent mortality, is associated with decreasing dose, and that with increasing time and decreasing dose there is associated a changing but overlapping

TABLE II: CHARACTERISTICS OF THE ISOTOPES

Isotope	Energy (MEV)	Half-Life	Subsequent Radiations	Site of Major Deposition
Ra^{226}	4.8 α	1620 yr.	4 alphas within 4 days	Skeleton
Pu^{239}	5.15 α	24,300 yr.	(U-235, 7.1×10^8 yr.)	Skeleton, liver
Po^{210}	5.3 α	138.3 yr.	(stable lead)	Reticular tissues
U^{233}	4.8 α	1.62×10^5 yr.	(Th-229, 7,300 yr.)	Skeleton, kidneys
U^{232}	5.3 α	70 yr.	5.4 α, 1.9 yr.; 4 alphas within 4 days	Skeleton, kidneys
Th^{228}	5.4 α	1.9 yr.	4 alphas within 4 days	Reticular tissues
Ru^{106}	0.04 β^-	1 yr.	3.5 β^-, 30 sec	Skeleton, liver
Sr^{89}	1.48 β^-	50 days	(stable Y)	Skeleton
Sr^{90}	0.54 β^-	28 yr.	2.18 β^-, 64.2 hr.	Skeleton
Y^{90}	2.18 β^-	64.2 hr.	(stable Zr)	Skeleton, liver
P^{32}	1.70 β^-	14.3 days	(stable S)	(General), skeleton
Ca^{45}	0.25 β^-	152 days	(stable Sc)	(General), skeleton

complex of disease processes. Briefly, in mice the acute irradiation picture encountered from ten through thirty to forty days blends into the subacute disease, which is often seen as late as one hundred and fifty to two hundred days after injection; tumors of the lymphoid tissues may appear in great number after one hundred days, and malignant bone tumors often may be the primary cause of death after one hundred and fifty days. In addition, the "background" of infectious, degenerative, and neoplastic diseases becomes relatively more important with time, so that the data plotted in this fashion tend to lose significance after three hundred to four hundred days.

No explanation for the fact that Ra^{226} was less effective than the other alpha-emitters as a killing agent for mice is evident from their physical properties (Table II). Nor is there any obvious reason why these isotopes of plutonium, polonium, thorium and uranium produced such similar results among themselves. It cannot be simply a matter of the energy of the alpha rays because the emanations of Ra^{226} and U^{233} have similar energies; nor is it a matter of half-life, since all except Po^{210} have half-lives much longer than the critical period under consideration here. It can be speculated that the similarities among the other alpha-emitters were accidental and that Ra was not more effective than it was because its radon daughter is a chemically inert gas, and it has ample time during its 3.8 day half-life to reach the lungs of an animal as small as the mouse; thus most of the four alpha radiations, which follow the decay of a Ra^{226} atom within four days, occur after the radon has been exhaled. It can be speculated further that the greater effectiveness of Pu^{239} was due to its greater retention, in addition to its more energetic alpha particle (5.15 MEV compared to 4.8 MEV for Ra^{226}). Perhaps Po^{210} and Th^{228} owe their greater efficacy to their more energetic rays and to their localization in reticular tissues, and U^{233} may owe its greater potency to the production of kidney injury.

The results obtained with the beta-emitters, on the other hand, can be interpreted in large part on the basis of energy and half-life. If it be assumed that the fifty-day half-life of Sr^{89} does not limit its acute toxicity, as measured by 50 per cent mortality in thirty days, then its 1.5-MEV beta may be equated to its LD 50/30 of 8 μc/gm. When these Sr^{89} data were used to predict the LD 50/30 of Ru^{106}, it was calculated by inverse proportions that, if 1.5 MEV = 8 μc/gm., then 3.5 MEV = 3.4 μc/gm.; Walton and Brues found the LD 50/30 to be approximately 3.5 μc/gm. (2). These Sr^{89} data were also used to predict the acute lethality of Sr^{90} in equilibrium with Y^{90}. Calculation based on additivity of the Sr^{90} beta (0.54 MEV) and its Y^{90} daughter beta (2.18 MEV) indicated an LD 50/30 of 4.4 μc/gm., while calculation based on the stronger radiation alone in-

dicated an LD 50/30 of 5.5 μc/gm. Since the experimentally determined dose was approximately 6 μc/gm., it appears that the weaker beta ray of Sr^{90} contributed nothing to the acutely lethal effect. Similar estimation for Ca^{45} indicated an LD 50/30 of 48 μc/gm., but none of the mice that received 49.6 μc/gm. died acutely, of Y^{90} was approximately 12 μc/gm. The available data on P^{32} compared with those on Sr^{89} indicate that the 14.3 day half-life of the former is sufficiently short to limit its toxicity. If this were not so, the highest dose used (7.36 μc/gm.) should have killed 50 per cent of the animals in thirty days rather than in one hundred

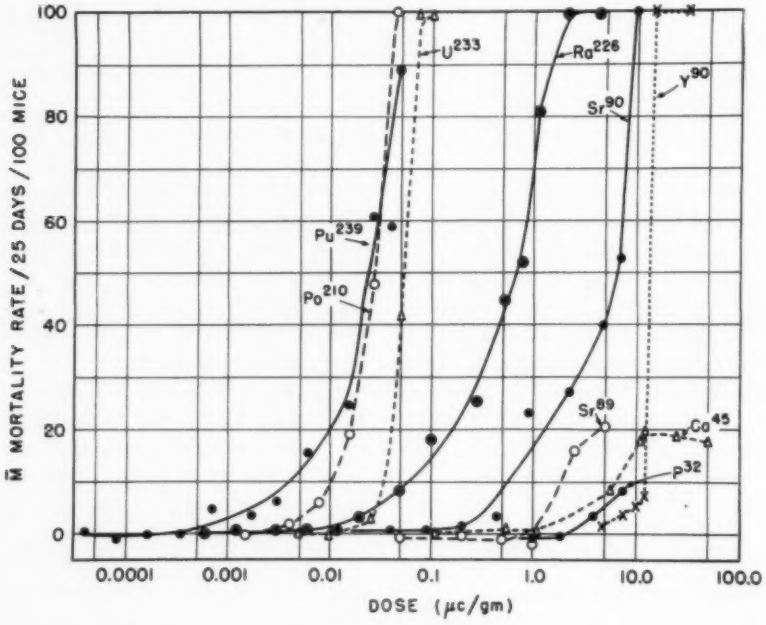

Fig. 3. Relationship between isotope dose and mortality rate.

although all showed subacute radiation symptoms. The shape of the LD 50 curve suggests that acute killing is not possible with such a weak beta-emitter. Further investigation of this problem with this particular isotope probably will not be undertaken, since enough Ca^{45} to treat 15 mice with 100 μc/gm. would cost between $1,500 and $2,000 at present rates.

The effect of half-life upon toxicity can be seen by comparing the curves for Sr^{90} and Y^{90} (Fig.1) since, as indicated above, their effective energies are probably the same but their half-lives are 28 years and 64.2 hours, respectively. From fifteen through one-hundred days, Y^{90} appeared to be half as potent as Sr^{90}; the LD 50/30 and twenty-five days, as was observed experimentally.

Although these data are not exhaustive, predictions of the LD 50 of other radioisotopes based upon them should be correct within a factor of 2. The addition of information on acutely lethal levels of U^{232} would greatly facilitate future guessing about alpha-emitters, and the inclusion of data on P^{32} at about 15 μc/gm., as well as on an inexpensive, weak beta-emitter with a non-radioactive daughter, would be of value. It appears that, in general, among the beta-emitters those with relatively long half-lives are twice as effective as lethal agents during the acute period as those with very short half-

lives (*e.g.*, Sr^{90} *vs.* Y^{90} and Sr^{89} *vs.* P^{32}), and that there is a direct relationship between energy and lethality, at least where moderate and high energies are involved (*e.g.*, comparisons among Ru^{106}, Sr^{90}, and Sr^{89}). The distribution of the radioelements within the body and their retention seem to be relatively unimportant when acute lethality is the criterion of effect. In evaluating chronic radiotoxicity, however, these factors are of major concern.

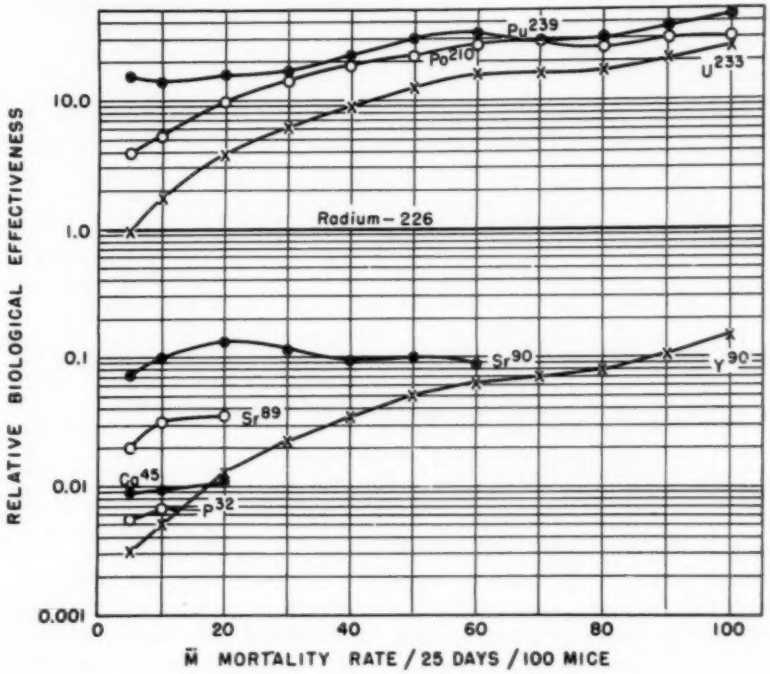

Fig. 4. Biological effectiveness relative to radium in increasing net mean mortality rate.

Mortality Rates: Comparisons of life expectancy and tumor probability, which have been shown to be valuable tools in assessing RBE (1), cannot be made until the last experimental animal has died. Since this situation probably will not obtain for at least another year in the current experiments, comparisons of crude mortality rates and of mortality rates with lymphoid tumors and with malignant bone tumors seem a profitable approach at this time. For each isotope dose the average rates per 100 animals at twenty-five-day intervals up to four hundred and twenty-five days after injection were calculated. In order to minimize the influence of infectious diseases and possible environmental accidents, which may vary markedly from experiment to experiment, the average rate displayed by each experimental group was corrected by subtracting from it the average rate for its specific control population to give a net average.

These net average mortality rates are plotted against dose in Figure 3, and it is seen that the same general order obtains as when the time to 50 per cent mortality was plotted against dose. The doses of Sr^{89} and P^{32} were not large enough to result in high mortality rates, and the inability of Ca^{45} to kill acutely is again illustrated. When the radium curve is converted to unity and the others are plotted accordingly, the effectiveness of the various isotopes relative to radium in increasing the

mortality rate becomes more clear (Fig. 4). This method of representation permits extrapolation toward indifference doses, and it emphasizes the changing RBE with changing degree of response. Thus, it is seen that the potency of Ra^{226} at the lowest measured mortality rate was equal to that of U^{233}, 1/4 that of Po^{210}, which is localized in the reticular tissues, P^{32}, which initially is distributed throughout the body, or Y^{90}. The latter isotope resembled x-rays in its effects in that animals that did not die within thirty days apparently recovered but displayed a very high incidence of lymphoid tumors at a later time.

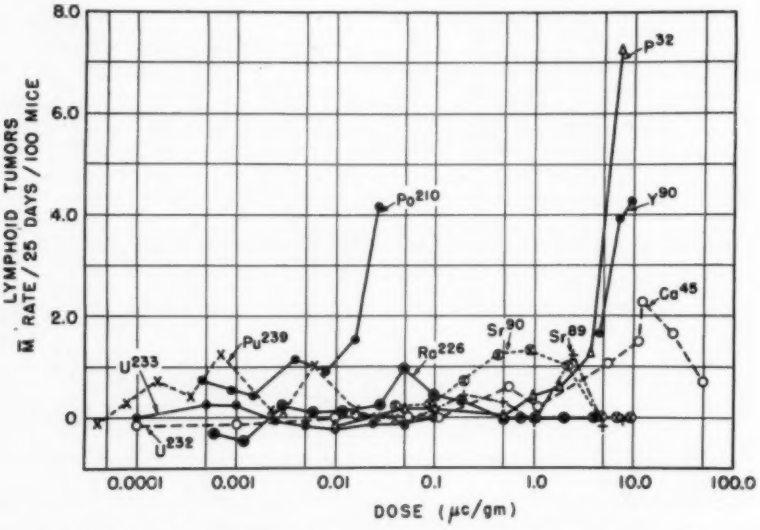

Fig. 5. Relationship between isotope dose and net rate of mortality with lymphoid tumors.

and 1/15 that of Pu^{239}, whereas at more toxic levels radium was only 1/20 to 1/45 as effective as the others. On the other hand, the efficacy of Sr^{90} remained about 1/10 that of Ra^{226} over the range studied.

Definitive conclusions cannot rest on average mortality rates restricted to death with lymphoid tumors or bone tumors when these rates are limited to four hundred and twenty-five days after injection, since neoplasms of both types may appear in large number after that time among the animals of the moderate and low dosage groups. However, they give some indication of what the final comparisons will show. In Figure 5 it is seen that appropriate doses of Pu^{239}, Ra^{226}, Sr^{89}, Sr^{90}, and Ca^{45} increased the average rate of mortality with lymphoid tumors, but these bone-seekers were not nearly as effective in this respect as Po^{210},

The superiority of Sr^{90} over Sr^{89} as an inducer of malignant bone tumors was evident by four hundred and twenty-five days (Fig. 6), and, in spite of its low toxicity in terms of acute lethality, Ca^{45} proved to be a potent skeletal carcinogen. During this period, the tumor rates among the animals that received the alpha-emitting bone-seekers were considerably lower than the rates among those that received beta-emitters; these data will be brought into proper perspective when total tumor incidences and tumor expectancies can be compared. Treatment with Po^{210} and P^{32} resulted in a few malignant bone tumors, but the rates were too low to be graphically presented here. These data, even though preliminary, have some value in indicating RBE. For example, in round figures at a death rate of 10 bone-tumor-bearing mice per twenty-five days per 100 animals, Pu^{239} was twenty

times as effective as Ra^{226} and Ra^{226} was five times as effective as Sr^{90}, ten times as effective as Sr^{89}, and fifty times as effective as Ca^{45}.

SUMMARY

1. The acute and chronic toxicity of internally deposited radioisotopes is being studied in CF1 female mice under standardized conditions.

2. All the alpha-emitting isotopes that have been tested are approximately twenty times as effective as radium 226 (on the basis of dose injected per unit weight) in killing half of the population in twenty to thirty days. This result is not readily explainable in terms of particle energy, physical half-life, biological half-time, or tissue distribution, but these factors may be operating none the less.

3. The beta-emitting isotopes that have been tested are less potent killing agents at acutely lethal levels than Ra^{226}. Their relative effectiveness can be interpreted in large part on the basis of energy and half-life; those with relatively long half-lives are approximately twice as lethal as those with very short half-lives, and there appears to be a direct relationship between energy and lethality. Tissue distribution and retention seem to be relatively unimportant when acute lethality is the criterion of effect.

4. Comparisons of net average mortality rates from the time of injection to four hundred and twenty-five days later show increasing values of relative biological effectiveness with increasing mortality rate. At the lowest measured rate the ratios were $15(Pu^{239}):4(Po^{210}):1(Ra^{226}):0.07(Sr^{90}):0.02(Sr^{89})$.

5. During the first four hundred and twenty-five days there was a perceptible increase in mortality rate with lymphoid tumors among the animals that received appropriate doses of Pu^{239}, Ra^{226}, Sr^{89}, Sr^{90}, and Ca^{45} and a pronounced increase among those that received Po^{210}, P^{32}, and Y^{90}.

6. Tentative figures for relative effectiveness in inducing malignant bone tumors based on an average rate of 10 deaths

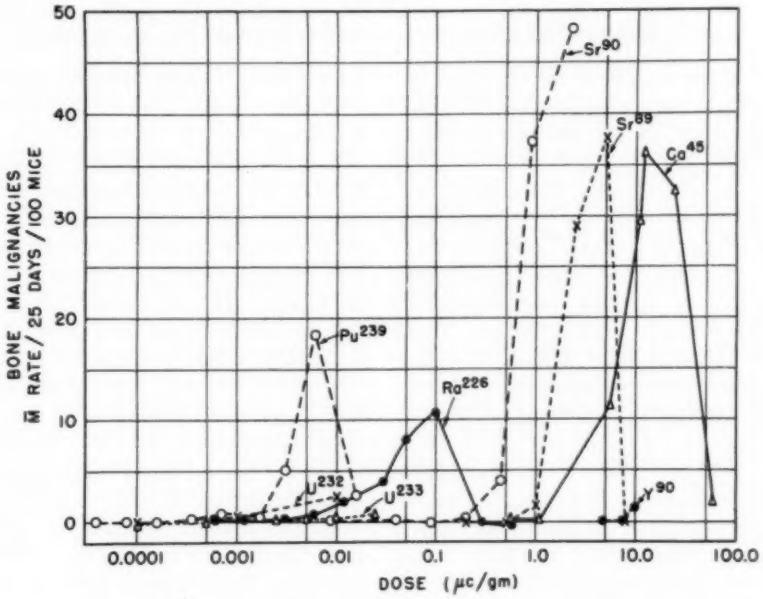

Fig. 6. Relationship between isotope dose and net rate of mortality with malignant bone tumors.

with bone tumors per twenty-five days per 100 animals, are 20(Pu^{239}): 1(Ra^{226}): 0.2(Sr^{90}):0.1(Sr^{89}):0.05(Ca^{45}).

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Argonne National Laboratory
Lemont, Ill.

SUMARIO

Relativa Eficacia Biológica de Algunos Emisores de Radiación Interna

En un estudio corriente de la toxicidad aguda y crónica de radioisótopos depositados internamente en ratones, los emisores alfa empleados (Po^{210}, Th^{228}, Pu^{239} y U^{233}) resultaron ser veinte veces más eficaces que el Ra^{226} (a base de dosis inyectada por unidad de peso) para matar la mitad de la población en veinte a treinta días. Este resultado no se explica fácilmente en términos de energía de partículas, hemi-vida física, hemi-tiempo biológico o distribución histológica, aunque estos factores pueden, sin embargo, intervenir.

Los isótopos emisores de rayos beta (Ca^{45}, P^{32}, Sr^{89}, Y^{90} y Ru^{106}) se mostraron menos potentes que el Ra^{226} como destructores a concentraciones agudamente letales. Los de hemi-vidas relativamente largas manifestaron una letalidad aproximadamente doble que la de los de hemi-vida muy corta, y aquí tampoco pareció haber relación directa entre la energía y la letalidad.

Las comparaciones de los coeficientes de mortalidad media neta desde la fecha de la inyección del isótopo hasta el 425° día después revelaron cifras crecientes de relativa eficacia biológica con el crecimiento del coeficiente de mortalidad.

Durante los 425 días consecutivos a la inyección hubo un aumento perceptible en el coeficiente de mortalidad por tumores linfoideos entre los animales que recibieron dosis apropiadas de Pu^{239}, Ra^{226}, Sr^{89}, Sr^{90} y Ca^{45} y un aumento destacado entre los que recibieron Po^{210}, P^{32} e Y^{90}.

Cifras tentativas para la eficacia relativa en la inducción de tumores óseos malignos son 20 para Pu^{239}, 1 para Ra^{226}, 0.2 para Sr^{90}, 0.1 para Sr^{98} y 0.05 para Ca^{45}.

DISCUSSION

Gioacchino Failla, Sc.D. (New York, N. Y.): This kind of work is very important to the Atomic Energy Commission and will be, in the future, to industrialists concerned with the atomic problem, because it determines the permissible limits of radioactive material in air or water that can be allowed for human consumption. In that sense, I think it is perfectly satisfactory to refer to this in terms of biological effectiveness. On the other hand, from the point of view of radiobiology, shall we say, it is not proper to speak of an RBE if the radioactive material acts on different organs. Following this approach you could just as well have an RBE for, say, x-rays and exposure to carbon dioxide, in which case there would be no ionization involved at all. When one radioactive isotope acts on liver and spleen and kidney and another one acts on the bone, they both kill the animal, but the mechanism is entirely different. It is not proper to speak of an RBE under those circumstances, although it is true that a related concept is used here for the protection of persons who might ingest radioactive material.

The Relative Biological Effectiveness of Fast-Neutron and X-Radiation

Survival and Cataract Studies of Swiss Mice[1]

E. F. RILEY, Ph.D., T. C. EVANS, Ph.D., R. B. RHODY, Ph.D., P. J. LEINFELDER, M.D., R. D. RICHARDS, M.D.

THE RELATIVE biological effectiveness (RBE) of fast-neutron and x-radiation is a concern of persons responsible for radiation safety measures, as well as those interested in the mechanisms of radiobiological action. The RBE of fast neutrons and x-rays has been found to vary when different criteria, different tissues, or different exposure patterns have been utilized in deriving the ratio (1, 2). In establishing an acceptable tolerance limit for neutron radiation, therefore, the most unfavorable effectiveness ratios must be considered. An earlier study by Evans (2) indicated that lens damage was one of the more critical biological effects of low-level neutron irradiation. Further study of the relative cataractogenic effectiveness of fast-neutron and x- or gamma radiation was then begun at this and other laboratories. Because the dosimetry of fast-neutron radiation had not been standardized, it seemed prudent also to determine a biological unit of exposure, the 30-day LD 50. This paper summarizes our observations on survival and cataract development after single exposures to several neutron sources as compared with observations after x-irradiation.

EXPOSURE METHODS

The animals utilized in all experiments were mice of an albino Swiss stock raised in our laboratory. At weaning time, the sexes were separated and put into stainless steel boxes, 8 mice of comparable age (no more than five days difference in date of birth) per box. The occupants of any one box were seldom all litter mates, thus tending to randomize the sampling. The sawdust in the boxes was changed three times per week; food and water were available at will. Mice from the stock colony were prepared for experimental use by clipping the toes to insure proper identification.

The mice were irradiated at two and a half to three and a half months of age. The several boxes housing mice of the same age (± two days) were usually divided into two groups, one group for neutron irradiation and the other for x-irradiation. The several boxes in each group were randomly assigned to dose levels scattered over the entire range of exposures under investigation. The animals arbitrarily chosen as controls were not irradiated, but were otherwise transported, confined, and handled like the irradiated animals. In similar fashion, mice of different ages within the range of two and a half to three and a half months were allocated to the same or interspersed dose levels. With one exception (exposures to fission neutrons), experiments were repeated several times during a period of two to three years. The results of all repeated experiments have been combined for the final summary.

X-radiation: The studies of x-radiation effects, which have extended over a period of seven years, were begun with the following exposure factors: 200 kv, 5 ma, 0.25 mm. Cu plus 1.0 mm. Al external filtration (plus the inherent filtration of the glass envelope), 43 cm. distance from the target to the center of the mouse's body, and a rate of 33 r per minute. More recent data were obtained with a G. E. Maxitron and the following factors: 250

[1] From the Radiation Research Laboratory and the Department of Ophthalmology, State University of Iowa, Iowa City, Iowa. This work was done with aid from the U. S. Atomic Energy Commission under contract AT-(11-1)72 Project I, under recommendation of the Radiation Cataract Committee of the National Research Council. Presented in part at the Forty-first Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 11–16, 1955.

kv, 30 ma, 0.25 mm. Cu plus 1.0 mm. Al external filtration, 70 cm. distance, h.v.l. 0.99 mm. Cu, and an exposure rate of 75 r per minute. Exposures were measured with some scatter, a Victoreen 100-r chamber being placed in an empty exposure compartment surrounded on three sides by mouse-filled compartments. Such measurements were found to be 4 per cent greater than those in air. (This was done because measurements of neutron exposures included some scattered radiation, a meter being placed next to the animals for a continuous monitoring of each exposure.)

For survival studies, mice were irradiated on a turntable in compartments (1 3/8 × 1 3/8 × 4 inches) of a perforated plastic box. The animals were arranged in two rows with no more than 4 or 5 per row, in order to keep the variation in exposure less than 5 per cent. For cataract studies, mice were restrained in 50-ml. perforated plastic centrifuge tubes with a cork for the open end. After their first reaction to confinement, the animals settled down and did not try to turn around during irradiation. This permitted a shielding of the bodies with 1/8 inch of lead and an irradiation of heads only. The latter procedure was adopted when it was found necessary to exceed the whole-body lethal exposure levels in order to produce complete cataracts in 50 per cent of the eyes within one year. The arrangement here, also, was in two rows of 4 or 5 mice per row; the radiation was delivered unilaterally from above.

Fission Neutrons: A few mice were irradiated for us by Dr. Howard H. Vogel at Argonne National Laboratory. The neutrons were obtained by fission in a uranium converter plate placed at the opening of a thermal column at one of the reactors (3). For the purposes of the present study, the fission neutrons were considered to be a relatively low-energy neutron radiation, since the energy spectrum of this radiation had a peak at about 0.7 MEV (4). The mice were irradiated in compartments of a perforated Lucite box; exposures required ninety minutes. Since the results obtained with our own mice were not greatly different from those observed by Clark *et al.* (5), this series of exposures was not repeated.

37-Inch Cyclotron (University of Chicago): For the purposes of our study, the fast neutrons from the University of Chicago 37-inch cyclotron were also considered to be relatively low in energy. A thick beryllium target was bombarded with deuterons (9.5 MEV), producing neutrons (E_{max} about 13.5 MEV) by the reaction $Be^{9}(d,n)B^{10}$. Investigations of the energy spectrum at similar generators (6, 7, 8) suggest that most of the neutrons at the beam center were probably about 4 MEV. The neutrons utilized for irradiation, however, were degraded in energy by the lead filtration placed around the mice. Since a relatively thick filter was used (4 inches on the incident side), and since the cross section for scatter increases at lower energies, most of the neutrons utilized may have had energies of only 1 to 2 MEV.

Each irradiation was monitored by the integrator on the cyclotron control panel and a 100-r chamber of a Victoreen r-meter, the latter being placed inside the lead enclosure among the mice. The rep (roentgen equivalent physical, = 0.93 rad) per division as measured by the r-meter (2.2 rep per div. 100-r chamber) was determined by calibration against a tissue-equivalent chamber (9). A gamma contamination (7 to 15 per cent of the total dose indicated by the r-meter) was considered in establishing the roentgen equivalence of the r-meter readings. This method of dosimetry was also utilized for measuring the other neutron radiations in order to make a comparison of the biological effectiveness.

The mice were irradiated in a lead enclosure placed at the center of the neutron beam and 8 to 12 inches from the target. The lead enclosure was 4 inches thick on the incident side, 1 inch thick on top, and 2 inches thick on all other sides. At first, individual mice were restrained during

exposure by placing them in the compartments of a copper cage (see Fig. 2 in Ref. 2). Later, perforated plastic boxes with compartments measuring 1 3/8 × 1 3/8 × 4 inches were used. The mice were irradiated from the side, generally unilaterally, although they could turn around, and some did. Exposures in the lethal range usually required thirty to forty-five minutes, depending upon the operating condition of the cyclotron.

60-Inch Cyclotron (Argonne National Laboratory): Four neutron radiations, each presumably having a different energy spectrum, were utilized at this cyclotron. The four different radiations were obtained by using either deuterons or protons as the bombarding particles and by placing mice either at the center of the neutron beam or at 180° from the beam center. The combination of deuteron bombardment and placement at the beam center provided a neutron radiation which, for our purposes, was of relatively high energy. The other three combinations provided radiations with less energy, more or less intermediate to the high-energy radiation and the low-energy radiations from fission and the 37-inch cyclotron. Following a résumé of the exposure method, the four neutron radiations will be described in so far as is possible at present.

All mice were irradiated inside lead enclosures. The enclosure which was located at the center of the neutron beam was 120 inches from the target; it measured 16 × 6 × 6 inches inside, and was 3 inches thick on the incident side, 2 inches thick at the ends, and 1 inch thick elsewhere. The enclosure back of the target (180° from the beam center) was 36 inches from the target; it measured 12 × 6 × 6 inches inside and was constructed like the other enclosure except that 3 inches of lead was used for the end nearest the dee housing. The mice were restrained in 50-ml. perforated plastic centrifuge tubes, placed on a Masonite rack having three shelves, and oriented with their heads toward the target. Chambers of a Victoreen r-meter were placed with the thimbles above the heads of the mice inside the enclosure for a continuous monitoring of each irradiation. The intensity of the neutron radiations varied at different positions along the incident side of the enclosures, which were oriented with the longest dimension horizontal and perpendicular to the beam. Although the estimates of this disparity have varied when different dosimeters were used, 15 to 20 per cent seems to be a reasonable value for the variation in dose rate from center to end of the enclosures. Because of this variation, the mice of each dose group were distributed along the entire length of the Masonite racks so that each group would be subjected to the same percentage variation in exposure.

The neutron radiation obtained by use of the *(d,n) reaction* and the *beam center* provided neutrons with a maximum energy of about 25 MEV and a peak in the energy spectrum at about 7 to 8 MEV (6). Again, as at the smaller cyclotron, the energies of the neutrons utilized were degraded by the lead filtration. In this case, however, only 3 inches of lead were used, and the scatter cross sections were less at the higher energies. Therefore, about 5 to 6 MEV seems a plausible estimate of the modal energies of the neutrons employed. The rep per division registered on the r-meter was again determined by calibration against a tissue-equivalent chamber. This result was compared with the results obtained by several other methods of neutron dosimetry (10). The agreement was quite good, and a ratio of 1.8 rep per division was established for this radiation. The inevitable gamma contamination was variously estimated to be responsible for 5 to 11 per cent of the total dose. Exposures in the lethal range, with 2 or 3 interruptions for r-meter readings, required thirty to forty minutes.

When the *180° position* was utilized with the *(d,n) reaction*, it may be presumed that the neutron energies were considerably less than at the beam center (11). Furthermore, since the cross section

TABLE I: THIRTY-DAY SURVIVAL, X-RADIATION
(Swiss Mice, Single Whole-Body Exposure)

Exposure (r)	Proportion Surviving Male	Female	Combined Survival (%)
A. 200-kvp x-radiation			
Controls	24/24	15/16	98
100–300	20/20	15/15	100
400–450	9/9	9/9	100
475	12/13	12/14	89
550	8/8	6/8	87
575	4/8		50
625	0/16	4/16	12
650	3/16		19
700	0/8	0/9	0
800–1000	0/34	0/14	0
B. 250-kvp x-radiation			
Controls	24/24	16/16	100
100–450		23/23	100
500	8/8	7/8	94
525		21/24	87
550	13/19	32/47	68
575	10/20	38/58	61
600	4/19	12/49	24
625	0/8	9/38	20
650	0/8	1/16	4
700–750	0/8	0/16	0

for scatter in lead is greater at lower energies, the lead filtration probably served to exaggerate the difference in energies of the neutrons utilized at the two positions, 0° and 180°. Again, measurements of exposure made with the r-meter were calibrated against a tissue-equivalent chamber. The results of this calibration were also compared with results obtained by other methods (10). The rep per division of the r-meter scale was almost the same as at the center of the neutron beam; a ratio of 1.8 rep per division was also used for this radiation. The gamma contamination at this position was estimated to be 10 per cent of the total r-meter reading. The exposure rate at 180° was only half that at the beam center. Nevertheless, because the radiation at 180° was biologically more effective than the radiation at the center of the neutron beam, exposures in the lethal range required only a little more time, forty to fifty minutes in all.

When mice were placed at the *center of the neutron beam* produced by *proton bombardment* of a beryllium target, most of the tissue dose was probably contributed by neutrons of less than 2.5 MEV. In support of this, it can be pointed out that (*a*) the Oak Ridge group, using 22-MEV protons, found that neutrons of 1.5 to 2.5 MEV contributed most to the tissue dose (12), and (*b*) protons of 11 MEV were employed for our study. Since the r-meter measurements of this radiation were not calibrated against any other neutron dosimeter, exposures can be given only in terms of "n," the amount of radiation discharging our 100-r chamber 1 scale division. The biological data obtained are nevertheless being included because, in a general way, they afford a comparison with the results observed by the Oak Ridge group. Exposure procedures were the same as were used at the center of the beam produced by the (d,n) reaction; because of the low intensity of this radiation, exposures in the median lethal range required about five to six hours.

A few animals were irradiated at *180° from the center* of the neutron beam produced by *proton bombardment* of the target. At the 180° position, the LD 50 was somewhat less than at the center of the beam. There was also a difference in the rate of exposure, the rate at 180° being 10 per cent less than at the beam center. These differences were not as great, however, as were observed when deuterons were used to generate neutrons. This may be explained, in part at least, by the observation that the (p,n) reaction seems to be less directional than the (d,n) reaction (11). On this basis, it may also be surmised that there was less difference in the energies of the neutrons front to back when protons were employed than when deuterons were used.

RESULTS: SURVIVAL

Tables I–IV (in the order of increasing energy) and Figure 1 summarize the thirty-day survival data obtained after single-dose whole-body irradiation of Swiss mice. In each table, the number of each sex surviving is shown as a fraction of the number of that sex irradiated. The last column in the table gives the percentage of the total number (both male and female)

that survived at the different exposure levels. In Figure 1, the percentages surviving have been plotted as a function of exposure, and survival curves have been fitted visually to the data as plotted.

As stated before, the survival data used to derive the LD-50 values were the combined results of several experiments

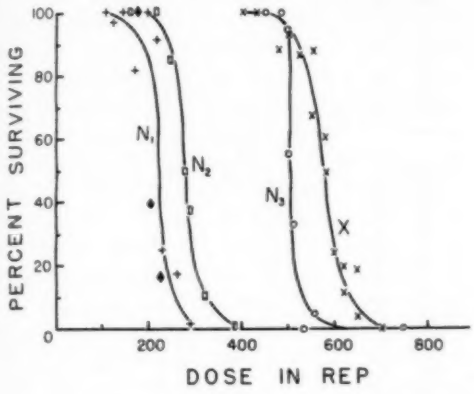

Fig. 1. Thirty-day survival of Swiss mice after single, whole-body exposure to neutron or x-radiation.

N_1. "Low-energy" neutrons (diamonds = fission, plus signs = 37-inch cyclotron).
N_2. "Intermediate-energy" neutrons (squares = 60-inch cyclotron, 180°).
N_3. "High-energy" neutrons (circles = 60-inch cyclotron, beam center).
X = 200 and 250-kvp x-radiation.

done over a period of years; in general, each of the experiments consisted of a graded series of single exposures scattered over the entire range being investigated. Although there are objections to combining data in such a manner, certain practical limitations made it necessary to accumulate cataract data in this piecemeal fashion. So, as a check on the constancy of various biological, physical, and procedural factors during the period of cataract study, survival data were accumulated concurrently and in a parallel manner.

X-Radiation: Table I summarizes the thirty-day survival data observed after exposure to x-radiation of 200 kvp (Part A) or 250 kvp (Part B). The 200-kvp radiation, with considerable inherent filtration, and the 250-kvp radiation were

TABLE II: THIRTY-DAY SURVIVAL, FAST-NEUTRON RADIATION FROM 37-INCH CYCLOTRON OR FISSION
(Swiss Mice, Single Whole-Body Exposure)

Exposure ("n" rep)		Proportion Surviving Male	Female	Combined Survival (%)
A. Fission neutrons, Argonne National Laboratory converter				
Controls		7/7		100
175		12/12		100
205		4/10		40
227		1/6		17
B. 37-inch cyclotron, beam center				
Controls		24/24	16/16	100
20	45	15/15		100
40	90	8/8	6/6	100
50	110	20/20	18/18	100
60	130	21/22	8/8	97
70	155	16/16	20/20	100
80	175	12/17	23/26	82
90	200	20/20		100
100	220	19/21	6/6	92
110	240	2/8		25
120	265	0/13	4/9	18
130	290	0/12		0
150	330	0/5	0/9	0
175	385	0/8		0

probably equally penetrating in the mice. Accordingly, survival percentages have been depicted in Figure 1 with no distinction as to the peak energy of the radiations.

An LD 50 of about 575 r was indicated by each of three methods used to analyze the data: (*a*) the visually fitted survival curve in Figure 1, (*b*) the straight line visually fitted to the points obtained by plotting probability of survival, and (*c*) an analysis by the method of probits and fitting the curve by the method of least squares. Evaluation of the survival data also revealed no obvious change in the radiosensitivity of our mice during the period of study, and essentially no difference in their response to 200-kvp and 250-kvp radiations.

Fission Neutrons: The much greater biological effectiveness of fission neutrons, relative to x-radiation, is illustrated by the data of Table II (A) and the percentages surviving as plotted in Figure 1 (diamond symbols). The very limited data indicate an LD 50 of approximately 205 rep. This value agrees very well with the LD 50 of 210 rep observed by Clark *et al.* using CF1 female mice (5). This close agreement

TABLE III: THIRTY-DAY SURVIVAL, FAST-NEUTRON RADIATION, Be (p,n), 60-INCH CYCLOTRON
(Swiss Mice, Single Whole-Body Exposure)

Exposure ("n" rep*)	Proportion Surviving Male	Female	Combined Survival (%)
A. 180° from beam center			
Controls	39/39	8/8	100
83 150	11/12		92
118 210	13/14	8/8	96
156 280	7/20		35
B. Beam center			
Controls	(see Part A.)		100
55 100	5/5	6/6	100
100 180	17/17	16/16	100
120 215	34/34	4/4	100
140 250	9/9	13/13	100
175 315	9/12	12/14	81
240 430†	0/8	0/7	0

* Assuming 1 "n" = 1.8 rep (see p. 675).
† The first third of this exposure was atypical because of residual deuteron contamination in the dees.

TABLE IV: THIRTY-DAY SURVIVAL, FAST-NEUTRON RADIATION, Be (d,n) 60-INCH CYCLOTRON
(Swiss Mice, Single Whole-Body Irradiation)

Exposure ("n" rep)	Proportion Surviving Male	Female	Combined Survival (%)
A. 180° from beam center			
Controls	57/57	32/32	100
30 55		16/16	100
60 110		24/24	100
90 160		24/24	100
120 215	8/8		100
135 240	8/8	6/8	87
150 270		11/22	50
160 290		13/34	38
175 315		2/18	11
210 380	0/8		0
B. Beam center			
Controls	(See Part A.)		100
20 35	8/8	56/56	100
40 70	8/8	18/18	100
60 110	18/18	4/4	100
70 125	14/14	31/31	100
90 160	20/20	24/24	100
115 210	14/14	32/32	100
135 240	15/15	8/8	100
155 280	20/20	12/12	100
175 315	11/11	10/10	100
200 360	13/13	16/16	100
237 430		8/8	100
260 470		8/8	100
265 480		15/16	94
270 485		9/16	56
275 495		5/15	33
285 515		0/14	0
300 540	0/13	2/25	5
400 720	0/12	0/15	0
500 900	0/15	0/14	0

may be fortuitous, but it does suggest that the mouse strains used at the respective laboratories did not differ markedly in their radiosensitivity. Because of this apparent similarity in the response of the two strains, the irradiation of our strain was not repeated. Since the LD 50 reported by the group at Argonne National Laboratory was based upon much more extensive data, and since their value was essentially the same as the approximation derived with our own mice, the LD 50 for this radiation will be considered to be 210 rep for subsequent comparisons in this paper.

37-Inch Cyclotron: The survival data obtained after exposure to the neutron radiation of the smaller 37-inch cyclotron are presented in Table II(B) and in Figure 1 (the plus symbols and curve N_1). The data indicate an LD 50 of approximately 230 rep. On the basis of the respective LD-50 values, the neutron radiation from fission would seem to be a little more effective than the neutron radiation utilized at the small cyclotron. However, because of the uncertainties involved, we cannot be sure that there was actually any difference in the lethality of the two radiations.

60-Inch Cyclotron (d,n), 180°: The LD 50 for radiation from the 60-inch cyclotron, 180° from the center of the beam, appears to be about 280 rep. Three methods (see X-radiation, p. 667), were also used to determine this LD 50. The data upon which it is based are presented in Table IV (A) and Figure 1 (rectangular symbols and curve N_2). It seems quite probable, especially when the data of the high-energy neutron radiation are considered, that the radiation at 180° actually was less effective than the neutron radiation from fission or the smaller cyclotron.

60-Inch Cyclotron (d,n), 0°: The relatively high-energy neutron radiation from the 60-inch cyclotron at the beam center proved to be much less effective, biologically, than any of the other neutron radiations. Survival data obtained with this radiation are presented in Table IV (B) and Figure 1 (circle symbols and curve N_3). The LD 50, again derived in

three ways, seems to be about 490 rep. The survival curve (N_3) is also interesting in that it is unusually abrupt. This steep portion of the curve is based upon data obtained from three separate experiments done on different dates. Despite the possible errors due to a shifting of the beam, the difficulty in relocating the lead enclosures precisely, and the inhomogeneity of the intensity in the enclosure, the results of the repeated experiments were remarkably consistent.

Although a comparison of LD-50 values was not our primary objective, it became a corollary that could not be ignored. Since the mice were irradiated in front and back of the target on the same date, the difference between 490 rep and 280 rep could hardly be attributed to a change in the response of our meter or some variation in the biological materials. Several neutron dosimeters were used to check the response of our meter to the two radiations (10); these calibrations ruled out the possibility that the difference in LD-50 values was due to a differential response of the r-meter. The most plausible explanation, then, seemed to be a dependence of biological effectiveness on neutron energy. Over the range of energies utilized in this study, the biological effectiveness decreased with increased energy of the neutron radiation.

60-Inch Cyclotron (p,n): Table III shows the survival data obtained when neutrons were generated by proton bombardments of the beryllium target. These survival data were not plotted in Figure 1, since no factor for converting r-meter readings to rep was established for these radiations.

At the beam center, the LD 50 appeared to be between 175 and 240 "n," with 190 to 200 "n" as a reasonable estimate. Assuming an "n"-to-rep conversion factor of 1.8 (the factor used with deuteron bombardments), the median lethal dose would seem to be somewhere between 340 and 360 rep. Upton, *et al.* (13), utilizing protons of 22 MEV as bombarding particles, have reported an LD 50 of 362 rep. Although we could not duplicate their exposure conditions exactly, the results seem to be of the same order. Therefore, the difference between their LD-50 value (360 rep) and our other values (210, 230, 280, and 490 rep) would not seem to be due to differences in procedure, dosimetry, or biological materials.

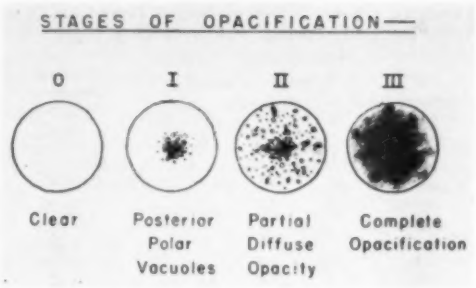

Fig. 2. Diagram representing stages of opacification observed in mouse lenses with ophthalmoscope.

At 180° from the center of the neutron beam produced by proton bombardments, the LD 50 appeared to be greater than 120 "n" and less than 155 "n." Again assuming the same rep/"n" ratio, the median lethal dose may be estimated to be about 250 rep. If this estimate is correct, the LD 50 for this radiation falls within the range of values obtained at the small cyclotron and at the 60-inch cyclotron utilizing the 180° position with the (d,n) reaction.

RESULTS: CATARACTOGENESIS

The lenses of all mice surviving thirty days after irradiation were examined with an ophthalmoscope. Survivors were reexamined at intervals over a period of twelve to fifteen months post-irradiation. Lens abnormalities were classified as follows: Stage 0, clear; Stage I, vacuoles collected at the anterior pole of the lens and/or vacuoles in the subcapsular cortex of the posterior polar region; Stage II, lens cortex diffusely vacuolated but still giving a red reflex; Stage III, complete opacification with no red reflex observable. The stages are diagrammatically represented in Figure 2.

In the attempt to relate the amount of

TABLE V: OPACIFICATION OF MOUSE LENS ONE YEAR AFTER SINGLE EXPOSURE TO X-RADIATION, HEAD ONLY

Exposure (r)	Number of Lenses Stage 0	I	II	III	Average Degree of Opacification*
A. 200-kvp x-radiation, LD 50 = 575 r					
Controls	25	3			0.1
300	2	14			0.9
400		4			1.0
450		22			1.0
500		4			1.0
600		3	1		1.2
700		5	2	3	1.8
800		1	4	11	2.6
900				24	3.0
1000				18	3.0
1100				14	3.0
1200				16	3.0
B. 250-kvp x-radiation, LD 50 = 575 r					
Controls	13	12			0.5
100		8			1.0
300		8			1.0
700			4	4	2.5
800			4	3	2.4
850			1	7	2.8
875			1	10	2.9
900				6	3.0
1000				14	3.0

* Derivation of average explained in text.

lens damage to exposure level, one problem was to determine the average degree of damage in a group of mice exhibiting all three stages of injury. An arbitrary average degree of opacification was devised whereby the number of lenses in each stage was multiplied by the number of the stage (0, I, II, III) and the sum of the products was then divided by the total number of lenses. (Since the loss of vision in Stage III is much more than three times the loss of vision in Stage I, some power of the stage number might have been used. However, the selection of an appropriate power would also be arbitrary and no more self-explanatory. For this reason, the average degree was computed by the method described above; as such, it represents the average clinical status of the mouse lenses rather than the average loss of vision.)

Also arbitrary is the time after irradiation at which a summary of lens injury should be made. Considering the time required for most cataracts to develop, the numbers surviving, and the limitations of animal quarters, one year post-irradiation seemed the best time to summarize the damage to lenses of mice. Longer periods of observation would be required for a study of the slower growing lenses of some larger mammals.

One other point should be mentioned before more specific discussion of the cataract data. The absolute value of any median cataractogenic dose should be considered as more tentative than the LD-50 values. The reasons for this greater uncertainty are: (a) decreased numbers surviving, (b) the possible influence of such additional factors as general health, fighting, etc., and (c) the effect of corneal changes, making examinations difficult and possibly influencing cataract development. Nevertheless, since these difficulties were experienced in all groups, the median cataractogenic dose levels are useful in comparing the relative effectiveness of different radiations. In making such a comparison, however, any conclusions based upon small differences in CD-50 values should also be quite tentative. A median cataractogenic dose, or CD 50, is defined in this study as that exposure to an ionizing radiation which would produce complete cataracts in 50 per cent of the mouse eyes within one year after irradiation or, alternatively, the exposure resulting in an arbitrary average degree of opacification of 2.5.

X-radiation: Table V shows the number of lenses in the various stages of opacification at one year after a single exposure to x-radiation. Also shown in Table V is the arbitrary average degree of opacification. From these data, it appears that the CD 50 was about 775 r. Accordingly, for x-radiation, the CD 50 is about 1.35 times larger than the LD 50. In Figure 3, the average degree of opacification has been plotted as a function of exposure. The curve, which was visually fitted to the plotted data, has a plateau at the level of Stage I and extending from about 100 r to 400 or 500 r. Within this range, 100 to 500 r, the amount of damage to the lens increased slightly with increased exposure. However, in none of the lenses in this dose

range did cataracts develop which progressed to the more advanced stages. In fact, in some cases, the opacities even seemed to regress during the last months of observation. (This apparent regression may have been due to a consolidation of abnormal fibers at the lens poles.)

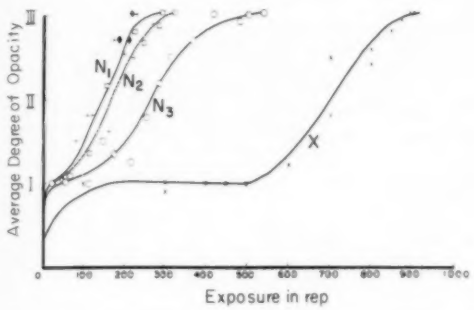

Fig. 3. Average degree of opacification (defined in text) observed one year after a single exposure to neutron or x-radiation.

N_1. "Low-energy" neutrons (diamonds = fission, plus signs = 37-inch cyclotron)
N_2. "Intermediate-energy" neutrons (squares = 60-inch cyclotron, 180°)
N_3. "High-energy" neutrons (circles = 60-inch cyclotron, beam center)
X. 200 and 250-kvp x-radiation

Fast-Neutron Radiation: For fission neutrons, the CD 50 would seem to be less than 175 rep. In contrast to the relationship observed with x-radiation, the cataractogenic dose of neutron radiation was less than the LD 50, in fact, less than 0.8 of the LD 50. The data (Table VI, A) are very limited but in line with our observations after other neutron irradiations.

The fast-neutron radiation of the 37-inch cyclotron yielded a CD 50 of approximately 180 rep. This value, again, was less than the LD 50, being roughly, 0.8 of that figure. The data obtained with this radiation are shown in Table VI, B, and in Figure 3 (plus symbols and the visually fitted curve N_1).

Enough data (Table VII, A) are available to show that the CD 50 was less than the LD 50 of the fast-neutron radiation at the center of the beam produced by proton bombardments. The best estimate that can be made would indicate that the CD 50 was about 0.6 of the LD 50.

TABLE VI: OPACIFICATION OF MOUSE LENS ONE YEAR AFTER SINGLE EXPOSURE TO LOW-ENERGY FAST-NEUTRON RADIATION

Exposure (rep)	Number of Lenses Stage 0	I	II	III	Average Degree of Opacification
A. Fission Neutrons, LD 50 = 210 rep					
Controls	11	1			0.1
175			5	13	2.7
205		1		5	2.7
227				2	3.0
B. 37-inch Cyclotron, LD 50 = 230 rep					
Controls	36	4			0.1
45		19	1		1.1
90		12		4	1.5
110		10	3	6	1.8
130		16	12	9	1.8
155		26	13	7	1.6
175			11	29	2.7
200			16	18	2.5
220			12	12	2.5
240				4	3.0
265			1	6	2.9

The neutron radiation at 180° from the center of the beam generated by deuteron bombardments produced complete cataracts in more than half the eyes exposed to 215 rep (Table VII, B). Estimating the CD 50 to be about 200 rep, it would be about 0.7 of the LD 50.

The CD 50 for the higher energy

TABLE VII: OPACIFICATION OF MOUSE LENS ONE YEAR AFTER SINGLE EXPOSURE TO FAST-NEUTRON RADIATION, 60-INCH CYCLOTRON, ARGONNE NATIONAL LABORATORY

Exposure ("n" rep)	Number of Lenses Stage 0	I	II	III	Average Degree of Opacification
A. (p,n) reaction, beam center, LD 50 = 190–200 "n"					
Controls	15	3			0.16
55 100*		4	2	1	1.6
100 180		5	4	3	1.8
110 200			4	4	2.5
120 215		2	2	8	2.5
145 230				10	3.0
175 315				30	3.0
B. (d,n) reaction, 180° position, LD 50 = 280 rep					
Controls	54	10			0.16
30 55		9	1		1.1
60 110		10	4		1.3
90 160		3	9	9	2.3
120 215			2	10	2.8
135 240		1	6	20	2.7
150 270			1	19	2.9
160 290				10	3.0
175 315				4	3.0

* Assuming 1 "n" = 1.8 rep (see 675).

TABLE VIII: OPACIFICATION OF MOUSE LENS ONE YEAR AFTER SINGLE EXPOSURE TO FAST-NEUTRON RADIATION, 60-INCH CYCLOTRON, ARGONNE NATIONAL LABORATORY

(Beam Center, (d,n) reaction, LD 50 = 490 rep)

Exposure ("n" rep)	Number of Lenses Stage 0	I	II	III	Average Degree of Opacification
Controls	57	17			0.23
10 20		47			1.0
20 35		48			1.0
30 55		32			1.0
40 70		32	1	1	1.1
60 110		29			1.0
80 145		15	2	5	1.5
100 180		18	8		1.3
120 215		19	6		1.2
140 250		6	17	2	1.8
155 280		8	13	7	2.2
175 315			9	8	2.5
200 360			13	25	2.7
235 425				10	3.0
260 470			2	33	2.9
275 495				14	3.0
300 540				4	3.0

neutron radiation appears to be about 320 rep (Table VIII and Fig. 3). When compared with the other neutron radiations, this higher-energy radiation proved to be the least effective in producing cataracts. It may be recalled that it was also the least effective of the neutron radiations when compared on the basis of thirty-day mortality. Again, as was the case with the other neutron radiations, the CD 50 was less than the LD 50, about 0.65 of the latter in this instance.

RELATIVE BIOLOGICAL EFFECTIVENESS

Table IX summarizes, for the different radiations, the estimates of median lethal and median cataractogenic exposures. Comparing the lethal and cataractogenic effectiveness of the neutron radiations, it appears that fission neutrons were most effective and the higher energy neutron radiation of the 60-inch cyclotron was the least effective. Relative to x-radiation, the RBE for lethality ranged from 2.7 to 1.2, and the RBE for cataract production from about 5.0 to 2.5. It would appear that the difference in biological effectiveness was inversely related to the modal energy of the neutron beams and probably directly related to the LET (linear energy transfer) (14) of the recoil particles produced by the various neutron radiations.

DISCUSSION

The results of our study have suggested that the higher-energy neutron radiations are biologically less effective. This seems to be true both for lethality and cataractogenesis. Upton, *et al.* (13) have summarized some earlier investigations of the biological effectiveness of neutron radiations. These earlier studies may also be interpreted as indicating that biological effectiveness is dependent upon the energy of the neutron radiation. If this hypothesis is correct, then acceptable neutron exposure limits based upon studies utilizing fission neutrons should also be acceptable for higher-energy neutron radiations within the limits of this study.

A second generalization which may be made from our findings is that for x-radiation the CD 50 is greater than the LD 50, while for neutron radiations the CD 50 is less than the LD 50. In fact, regardless of the neutron radiation utilized, the CD 50 seemed to be about 0.7 of

TABLE IX: RELATIVE BIOLOGICAL-EFFECTIVENESS OF SINGLE EXPOSURES TO FAST-NEUTRON OR X-RADIATIONS, BASED UPON SURVIVAL AND CATARACT DEVELOPMENT IN MICE

Radiation	Survival LD 50*	RBE	Cataractogenesis CD 50†	RBE
X-radiation	575 r	1.0	775 r	1.0
Fission neutrons	210 rep	2.7	<175	*ca.* 5.0
37-inch Cyclotron	230 rep	2.5	180–190 rep	4.5
60-inch Cyclotron (p,n) 180° (back)	240–260 rep‡	*ca.* 2.3	180–200 rep‡	4.0
Beam center	340–360 rep‡	*ca.* 1.6	190–200 rep‡	4.0
60-inch Cyclotron (d,n) 180° (back)	280 rep	2.1	200–210 rep	4.0
Beam center	490 rep	1.2	320–330 rep	2.4

* 30 day survival.

† Approximate exposure producing complete cataracts in 50 per cent in one year (average degree = 2.5).

‡ Assuming 1 "n" = 1.8 rep.

the LD 50. This relationship is illustrated in Figure 4, where the CD-50 values have been plotted as a function of the corresponding LD-50 values. In this figure the neutron data appear together in a group distinct from the x-radiation data. In this respect, the higher-energy neutron radiation retains the character

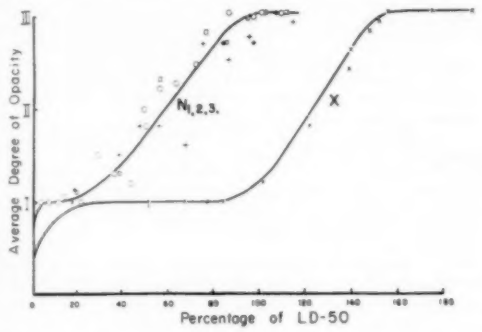

Fig. 4. Average degree of opacification plotted against percentage of LD 50.

N_1. "Low-energy" neutrons (diamonds = fission, plus signs = 37-inch cyclotron)
N_2. "Intermediate-energy" neutrons (squares = 60-inch cyclotron, 180°)
N_3. "High-energy" neutrons (circles = 60-inch cyclotron, beam center)
X. 200 and 250-kvp x-radiation

of neutron radiation even though it approaches x-radiation with respect to lethal effectiveness.

The higher-energy neutron radiation also retains its neutron character in another respect. Figure 5 shows that death after neutron irradiation occurred sooner than after x-irradiation. This has been observed previously (13, 15, 16) after exposures to other neutron radiations.

Another intriguing result of our study was the finding of a long plateau in the x-ray cataract curve (Fig. 3). This plateau is at the level of Stage I and extends from about 100 to 500 r. Within this range of exposures, damage to the lens appears to be limited and, at about six to eight months after irradiation, the lens seems to "recover." (The lens, of course, cannot get rid of any abnormal fiber elements which may have been formed. Recovery in this case seems to

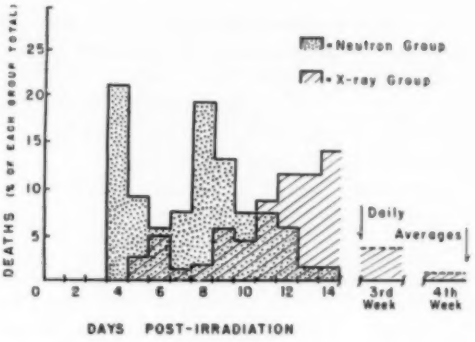

Fig. 5. Deaths per day (in per cent of total thirty-day mortality in each group) following irradiation. Exposures in the neutron group (68 deaths per 94 exposed) ranged from 465 to 550 rep. Exposures in the x-radiation group (163 died of 282 exposed) ranged from 550 to 650 r.

be a resumption of normal fiber production and a consolidation of the abnormal fiber elements at the lens poles.) A limited cataract development was also observed in rabbit lenses when exposures (up to 12,000 r) were restricted to 75 per cent of the lens or less (17). In a sense, both of these cases may be considered as partial irradiations, the latter being partial with respect to the entire lens structure and the former with respect to the minimum amount of general injury required to produce a progressive cataract. In contrast, the neutron cataract curves have a much less obvious plateau. The plateaus may indicate the range of exposures in which recovery is possible. The cataract curves, then, may illustrate the much greater chances for recovery after x-irradiation than after neutron irradiation.

SUMMARY

1. The LD 50 for Swiss mice exposed to x-radiation (single-dose, whole-body) was about 575 r.

2. Thec orresponding LD-50 values varied from 210 rep to 490 rep when different sources of neutron radiation were utilized.

3. The neutron RBE for thirty-day mortality, accordingly, varied from about 2.7 to 1.2.

4. The median cataractogenic dose of x-radiation (one year post-irradiation) appeared to be about 775 r.

5. The CD-50 values varied from less than 175 rep to about 320 rep with the use of the different neutron sources.

6. The neutron RBE for cataract production varied from about 5.0 to about 2.5.

7. Within the range of neutron energies utilized, the biological effectiveness (lethality and cataractogenesis) decreased with increased energy of the radiation.

8. The CD 50 was 1.35 times larger than the LD 50 when x-radiation was employed. Regardless of the source, the CD 50 for neutron radiations was less than the LD 50. The CD-50 values were approximately 0.6 to 0.8 of the neutron LD-50 values.

Radiation Research Laboratories
State University of Iowa College of Medicine
Iowa City, Iowa

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SUMARIO

La Relativa Eficacia Biológica de los Neutrones Veloces y la Radiación X. Estudios de la Sobrevivencia y las Cataratas en Ratones Suizos

Sumarízanse aquí observaciones relativas a la sobrevivencia y la formación de cataratas en ratones después de exposiciones aisladas a varios focos de neutrones, comparándose con las observaciones realizadas después de la irradiación X. Los resultados del estudio sugieren que las radiaciones de neutrones de mayor energía son biológicamente menos eficaces tanto en cuanto a letalidad como a cataratogenia.

Otra generalización derivada de estos hallazgos es que, para la radiación X, la DC 50 (la dosis necesaria para producir catarata en 50 por ciento de los animales) es superior a la DL 50, en tanto que, para las radiaciones de neutrones, la DC 50 es inferior a la DL 50.

Un tercer hallazgo fué la aparición de una meseta larga en la curva de catarata por rayos X, cuando se trazaba el índice de opacificación media observada al año de la exposición en relación con la dosis. La curva de catarata por neutrones reveló una meseta mucho menos destacada. Esto tal vez indique una probabilidad mucho mayor de curación después de la irradiación X que después de la irradiación con neutrones.

DISCUSSION

A. C. Upton, M.D. (Oak Ridge National Laboratory, Oak Ridge, Tenn.): I enjoyed this paper very much, as it presents data which are commensurate with our own. I should like to ask Dr. Evans if he thinks the RBE will increase appreciably with fractionation. I am not sure how his recent observations bear on this point. Will the RBE go up as the fractional dose goes down, and how high will it go?

Dr. Evans: I think I can answer the first question. It seems it will go up.

As to how high it will go I cannot say. I think probably the optimum condition would be of neutrons of a proper energy. We may, however, be all wrong on this. Some workers do not seem to find much difference with various energies that they have tried, but I can see that, if LET is what is working here, there should be an optimum or maximum one; then, if this effect is primarily on the chromosome (even in the "resting" condition), the maximum relative effect will come from optimal fractionation or protraction. I would certainly hate to guess how high it would go. It depends also on the biologic criteria. Even with the short recovery periods we have used, the effectiveness of the neutrons as compared with that of the x-radiation has apparently doubled.

It could go as high as 10.

Dr. Upton: I emphasize this question because, except for atomic disaster, where the exposure may be instantaneous in the case of those living in fallout fields or working around reactors or cyclotrons, the question of additivity or cumulative effect is perhaps the most important practical problem.

Gioacchino Failla, Sc.D. (New York, N. Y.): What do you think it should be for protection purposes? What value should be used?

Dr. Upton: That, I am afraid, is a loaded question. We are endeavoring in our own small way to find an answer for this question in the mouse. Experiments—those of Dr. Evans, Henshaw, Mitchell, and others—suggest that for reduction of life span the RBE for protracted radiation may well exceed 10, possibly even 20. For genetic injuries RBE's of the order of 10 or more do not seem unreasonable. We don't really know very much about RBE for tumor induction as a functional dose rate. I would say, in view of the lack of this information and the suggestion that RBE goes up around 10 or more, that for protection purposes an RBE of 10 is a very reasonable guess.

Dr. Evans: I might say that I have been a little concerned about the possibility that we may have to consider an accumulated exposure (rather than an acceptable level) in dealing with neutrons and particles of a high LET. I mean especially if the daily exposures are considerable. I hope this is an unfounded fear.

Howard H. Vogel, Jr., Ph.D. (Lemont, Ill.): I would like to point out that, although there seems to be evidence in this paper that there is no recovery from neutrons when cataracts are used as the end-point, if another biological end-point is employed, namely, thirty-day mortality, there definitely is some recovery. If one fractionates the neutron dose with different time intervals between paired doses, there is evidence of recovery. If one uses six-day intervals (and these results are preliminary) about 65 per cent of the first dose is recoverable after cobalt-60 gamma and only about 33 per cent after fission neutrons.

Harald H. Rossi, Ph.D. (New York, N. Y.): I would like to make a general comment about variations in LET distributions which are to be expected as neutron energy is varied. Because of the intrinsic nature of the Bragg curve, it can be shown that the LET spectrum of neutron dose varies rather markedly with neutron energy. In general, this spectrum will be heavily weighted at the low LET end when the neutron energy is high. As the neutron energy is decreased, more and more of the dose is delivered at lower LET until, at some rather low energy (perhaps 100 kv), there is again a reversal, with low LET components becoming once more evident. If it is assumed that RBE is closely related to LET, it must therefore be assumed that the biological effectiveness of neutrons is a rather complex function of neutron energy. This may explain apparent discrepancies among RBE values reported in the literature.

The Relative Biological Effectiveness of Neutrons, X-Rays, and Gamma Rays for the Production of Lens Opacities: Observations on Mice, Rats, Guinea-Pigs, and Rabbits[1]

A. C. UPTON, M.D., K. W. CHRISTENBERRY, M.D., G. S. MELVILLE, Ph.D.,[2] J. FURTH, M.D.,[3] and G. S. HURST, M.S.[4]

THE RELATIVELY high radiosensitivity of the lens of the eye to neutron radiation is now well established (Evans, 1948; Ham, 1953). In addition to experimental cataracts obtained in several species of neutron-irradiated laboratory animals, lens opacities have been observed in human beings exposed to cyclotron neutrons (Abelson and Kruger, 1949; Dollfus, 1950; Krause and Bond, 1951) and to fission neutrons from atomic detonations (Cogan *et al.*, 1949; Sinskey, 1955).

The growing prevalence in our environment of neutron sources such as high-voltage generators (cyclotrons) and reactors makes it increasingly important to know how much neutron radiation the human lens can tolerate. Furthermore, if neutrons are more effective than electromagnetic waves in causing lens opacities, precise comparison of the cataractogenic effects of these radiations should be made to further the knowledge of their fundamental radiobiologic differences.

This investigation was undertaken in an attempt to obtain quantitative information about the relative biological effectiveness (RBE) of neutrons, x-rays, and gamma rays for the production of lens opacities in several species of mammals.

METHODS AND RESULTS

Cyclotron Fast Neutrons: Mice, rats, and guinea-pigs were exposed in the Oak Ridge 86-inch cyclotron to neutrons having a mean effective energy of 1–2 MEV, obtained by the Be(p,n) reaction; the exposure facility and methods of dosimetry have been described in detail (Hurst *et al.*, 1956; Upton *et al.*, 1956). The cyclotron radiations were administered at a rate of 60 to 125 rep/min., contaminating gamma rays constituting approximately 5 to 15 per cent of the total dose in rep. Male and female mice of the RF strain, eight to fourteen weeks old, rats of a Wistar subline fifteen to eighteen weeks of age, and guinea-pigs[5] weighing 350 to 450 gm. were exposed in groups of 10 to 25 per dose level. After irradiation, the survivors were examined periodically for lens opacities with a Zeiss-Opton slit lamp, and the observations were scored according to a grading system described previously (Christenberry and Furth, 1951). For purposes of comparison, animals of corresponding age, sex, species, and strain were exposed to x-rays, with the following irradiation factors: 250 kvp, 30 ma, T.S.D. 93.7 cm., 70 to 80 r/min., filtration 3 mm. Al (Be window), h.v.l. 0.55 mm. Cu. RF mice were also exposed to Co^{60} gamma rays (1.1-1.3 MEV) at a rate of approximately 57 r/min.; the methods of exposure have been described (Upton *et al.*, 1956). Unless otherwise indicated, doses of radiation were administered in a single brief exposure of the whole body.

Lens opacities first became detectable within three to four months following irradiation, the rapidity of development and final severity of the opacities varying

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[2] 1st Lt., United States Air Force.

[3] Present address: Children's Cancer Research Foundation, 35 Binney Street, Boston 15, Mass.

[4] Health Physics Division, Oak Ridge National Laboratory.

[5] The authors are grateful to Dr. James B. Rogers, Department of Anatomy, School of Medicine, University of Louisville, Louisville, Ky., for supplying the guinea-pigs used in this study.

with the dose (Figs. 1–3). In all species these appeared initially as dot-like vacuoles in the posterior subcapsular region along the suture (grade +). The granular opacities gradually increased in density and coalesced to form radial streaks extending toward the equator; larger, irregular vacuoles were interspersed among them (grade ++). Concomitantly, there was consolidation about the posterior suture, resulting in a plaque-like opacity surrounded by a zone of haziness; this process was usually accompanied by the development of subcapsular vacuoles at the anterior pole. As the cataract advanced in severity, the posterior subcapsular opacity and surrounding zone of cloudiness increased in diameter, with extension of vacuoles and radial streaks farther toward the equator. Simultaneously, there was coalescence of the opacities at the anterior pole; occasionally, as much as three-fourths of the posterior subcapsular lamella was affected before there was detectable involvement of the anterior part of the lens. With further progression, the streaks radiating into the equatorial region extended anteriorly and joined with the expanding anterior subcapsular opacities (grade +++). As the cataract advanced to maturity, there was a gradual opacification of the entire cortex (grade ++++); the embryonic lens nucleus appeared to be unaffected in the several mature cataracts which were examined by sectioning of the lens.

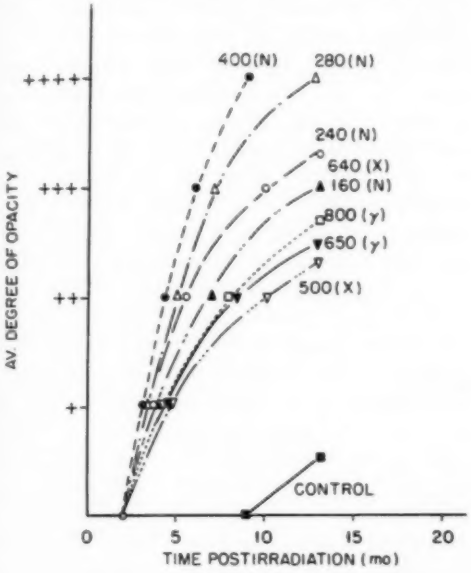

Fig. 1. Lens opacities in RF mice exposed to a single dose of cyclotron radiations (N), 250-kvp x-rays (X), or Co^{60} gamma rays (γ). The numbers denote doses in rep.

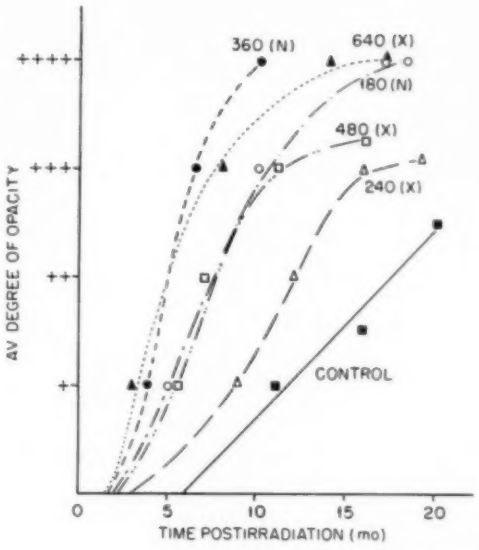

Fig. 2. Lens opacities in rats exposed to cyclotron radiations (N) or 250-kvp x-rays (X). The numbers denote doses in rep.

In addition to this sequence of changes, a "steamy" haziness of the lens was observed in conjunction with the appearance of the early posterior polar opacities in the animals exposed at the highest dose levels. This resulted from the formation of microscopic subcapsular vacuoles in both the anterior and posterior regions of the lens, producing a ring-like opacity at the equator. This opalescent appearance was observed in all three species but was more pronounced in guinea-pigs and, to a lesser extent, in rats.

At a given dose level, there was little variation among individuals of the same species; however, the progression was

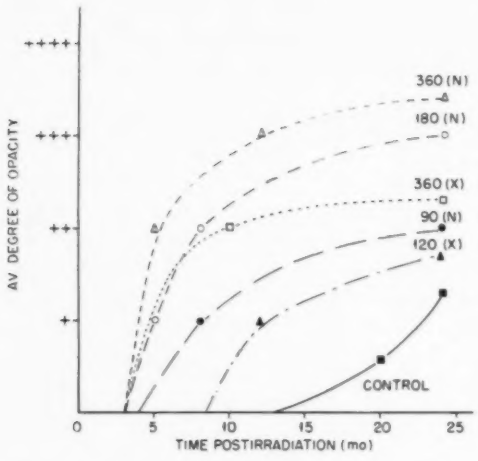

Fig. 3. Lens opacities in guinea-pigs exposed to cyclotron radiations (N) or 250-kvp x-rays (X). The numbers denote doses in rep.

more gradual in the guinea-pig (Fig. 3) than in the mouse (Fig. 1) or the rat (Fig. 2). The lens of the rat appeared the most sensitive to induction of mature cataracts. A comparison of the dose-response curves for all species (Figs. 1–3) indicates the high relative effectiveness of neutrons; in mice the response observed after 160 rep of neutron radiation was identical with that noted after 640 r of x-rays. At higher dose levels, neutrons produced mature cataracts (grade ++++), whereas such opacities did not occur with whole-body x-irradiation even at lethal levels. Under the conditions of this experiment, the LD 50/30 days for mice was approximately 360 rep of neutron radiation, 530 r of x-radiation, or 730 r of gamma radiation.

The RBE of the radiations for lens injury was also estimated by the method illustrated in Figure 4. Analyzed in this manner the neutron radiation was slightly more than three times as cataractogenic as x-rays and five times as effective as gamma rays, in mice. The RBE is defined herein as the ratio of the doses of the different types of radiation required for production of the same biologic effect, in this instance degree of lens opacity. Comparison of the dose-response curves for rats (Fig. 2) and guinea-pigs (Fig. 3) indicates a relative cataractogenic effectiveness of neutrons approximately two to three times that of x-rays.

Fission Neutrons from a Nuclear Detonation: Male and female LAF_1 mice, six to twelve weeks of age, were exposed to ionizing radiations from an experimental nuclear detonation. The animals were irradiated within (1) aluminum cylinders (for protection against blast and thermal injuries), in which they received predominantly high-energy gamma rays, or (2) in thick hemispherical lead shields, in which they received predominantly fission neutrons. Located at varying distances from the hypocenter of the explosion, the mice were exposed to graded doses of radiation (192 to 912 r); approximately four weeks after exposure, those surviving (more than 3,000) were transported to Oak Ridge; other details of the experiment have been reported (Furth *et al.*, 1954; Cronkite *et al.*, 1955). Female mice of the same age and strain were later exposed to x-rays, with the following factors: 230 kvp, 15 ma, T.S.D. 100 cm., filtration 1 mm. Cu plus 1 mm. Al, h.v.l. 1.93 mm. Cu, dose rate in air 14 r/min.[6]

The lens opacities observed in these mice (Fig. 5) were similar in appearance and rate of progression to those seen in the RF mice exposed to cyclotron radiations, x-rays, and Co^{60} gamma rays (Fig. 1). In general, however, the lens of the LAF_1 mouse appeared slightly more radiosensitive than that of the RF strain, exhibiting a greater degree of opacification for a given dose of radiation; thus mature cataracts (grade ++++) developed in the LAF_1 mice after 500 r of x-rays, a dose substantially below the LD 50/30 days. Comparison of the dose-response curves (Fig. 5) indicates that the fission neutrons were approximately two to three times as

[6] The breeding, irradiation, and transportation to Oak Ridge of the LAF_1 mice exposed to fission radiations and to x-rays were carried out by many investigators from laboratories of the Atomic Energy Commission and Armed Forces. Their contribution to these studies is gratefully acknowledged. The authors are particularly indebted to Dr. W. H. Langham and Dr. P. S. Harris for dosimetric data.

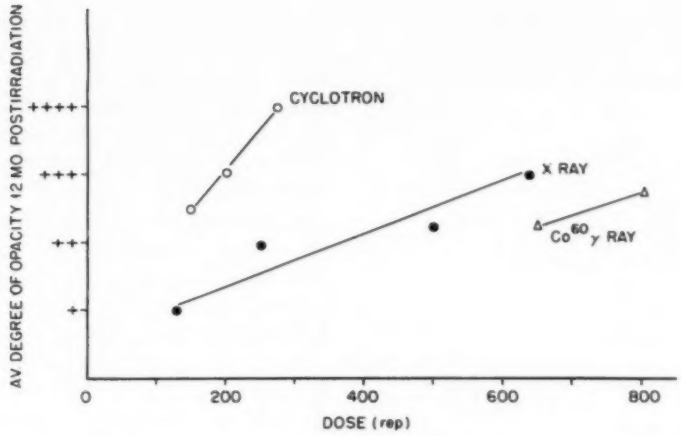

Fig. 4. Comparison of severity of opacities observed twelve months post-irradiation in RF mice exposed to cyclotron fast neutrons, 250-kvp x-rays, or Co^{60} gamma rays.

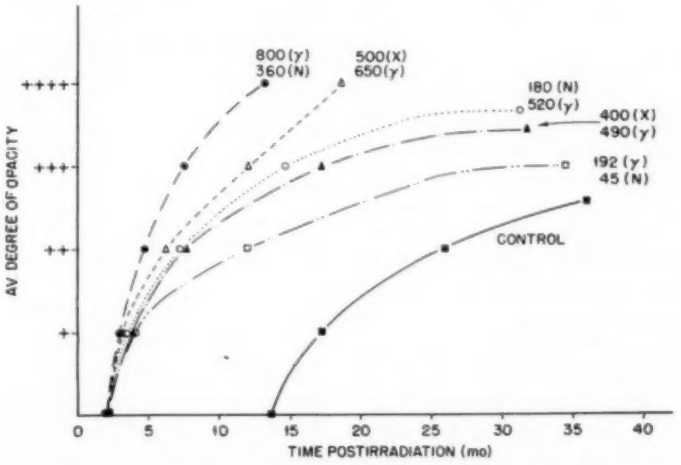

Fig. 5. Lens opacities in LAF_1 mice exposed to a single dose of fission neutrons (N) or gamma rays (γ) from an experimental nuclear detonation or to 250-kvp x-rays (X). The numbers refer to doses in rep. The neutron doses were calculated from the best physical measurements now available (P. S. Harris, personal communication) and are in agreement with estimates based on *Tradescantia* (A. D. Conger, personal communication).

effective as x-rays and two to more than four times as effective as gamma rays in causing lens opacities in the LAF_1 mouse, under the conditions of this experiment, the RBE increasing with decreasing dose.

Fast Neutrons from a Po-B Source: Neutrons produced by the B(α,n) reaction, having a mean effective energy of 2 to 3 MEV and with relatively little contaminating gamma radiation (<10 per cent)[7] were administered to RF mice twelve to eighteen weeks old, rats of a Wistar subline eight to fourteen weeks old, and Dutch hybrid and albino rabbits

[7] The neutron source was supplied by Dr. K. Z. Morgan, Health Physics Division, Oak Ridge National Laboratory.

TABLE I: LENS DOSAGE IN EXPERIMENTS WITH 2.5-MEV (Po-B) NEUTRONS

Species	Doses of radiation administered to lens		
	250-kvp X-rays* (r)	Co^{60} Gamma Rays (r)	2.5-MEV (Po-B) Neutrons (rep)
RF mice	33	33	0.373
	100	100	1.22
	333	333	3.73
		100 (10 r daily)	12.2
		100 (10 r at 3-day intervals)	37.3
		100 (10 r weekly)	37.3 (3.73 rep daily)
			37.3 (3.73 rep at 3-day intervals)
			37.3 (3.73 rep weekly)
Wistar rats	333		37.3
	100		12.2
	33		3.73
	10		1.33
Rabbits	333		37.3
	100		12.2
	33		2.4

* h.v.l. 0.55 mm. Cu.

twenty to thirty weeks of age. The source was calibrated at the beginning of the experiment with a "long" BF_3 counter. The dose in rep was calculated from the total neutron flux by use of the first collision dose curve (Hurst, 1954) and subsequent dosimetry accomplished by varying the source-to-lens distance to allow for the "inverse-square" attenuation of the neutron flux, with correction for decay of the polonium. Because of the low maximal intensity of the neutron radiation, the eyes of the animals were placed in close approximation to the source (3 to 5 cm.); nevertheless, the dose rate was relatively low (1 to 4 rep/hr.), limiting the total dose that could be administered in a single exposure (Table I). In addition to the neutron-irradiated group, animals of corresponding age, sex, species, and strain were exposed to Co^{60} gamma rays and to x-rays, at a rate of approximately 3 r/min. Rats and mice were exposed in groups of 10 to 20, and rabbits in lots of 3 to 8 per dose level (Table I).

In this experiment, x-ray and gamma rays appeared equally effective at the dose levels tested (Fig. 6). The opacities produced in mice by 37 and 12 rep of neutron radiation were indistinguishable from those caused by 333 and 100 r of x-rays (or gamma rays), respectively (Fig. 6), the RBE for neutrons being approximately 9 under these conditions. Furthermore, after only 1.3 rep of neutrons or 33 r of gamma rays, significant effects were

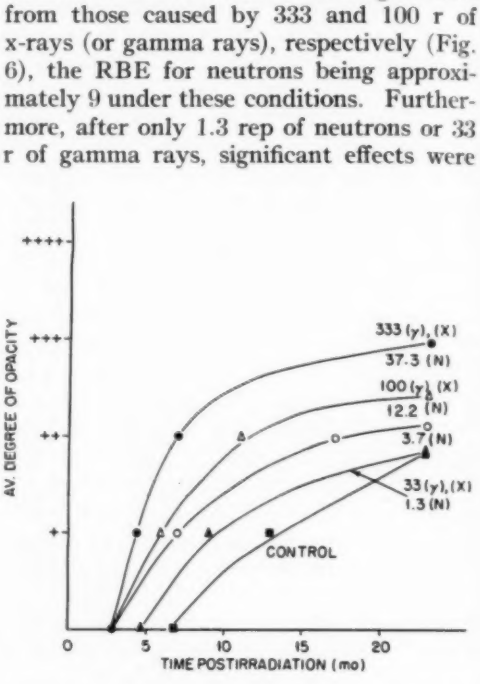

Fig. 6. Lens opacities in RF mice exposed to Po-B neutrons (N), Co^{60} gamma rays, (γ), or 250-kvp x-rays (X). The numbers denote doses in rep.

detected in mice, the RBE for neutrons appearing to be higher at the lower (threshold) levels (Fig. 6); these doses, however, caused but minimal opacities, which did not advance beyond those developing in the controls somewhat later. With fractionation of the neutron or gamma radiation, there appeared to be a slight reduction in the effectiveness of the total dose, but this difference was not marked even when the dose was administered in ten exposures, separated by intervals of one week; its significance is uncertain.

In rats exposed to 12 to 37 rep of neutrons, mild posterior polar opacities appeared, occurring slightly earlier than those developing spontaneously in the aging controls; in the animals exposed to 333 r of gamma rays there were no detectable lens changes.

In the rabbits, which have been followed for three years since irradiation, no opacities have been observed.

Thermal Neutrons: In order to compare the biological effects of slow neutrons with those of x-rays, RF mice were exposed to thermal neutrons in the thermal column of the Oak Ridge graphite reactor and to 250-kvp x-rays (Christenberry and Furth, 1951; Upton, Furth, and Christenberry, 1954). Precise quantitative comparison of the two types of radiation is complicated by uncertainties in the slow neutron dosimetry. The dose conversion for thermal neutrons depends on the size of the animal; the conversion factor used in this experiment was that determined by Brennan *et al.* (1954), based on the calculations of Conger and Giles (1950). It is noteworthy that the thermal column radiations were significantly more damaging to the lens then doses of x-radiation equivalent in thirty-day lethality (Fig. 7). Accordingly, since the RBE of thermal neutrons was calculated to be 1.7 for acute lethality (Brennan *et al.*, 1954; Upton *et al.*, 1954), it is probable that the RBE for lens injury is in the neighborhood of 3 to 6, a value not inconsistent with that of Storer and Harris (Harris, 1954).

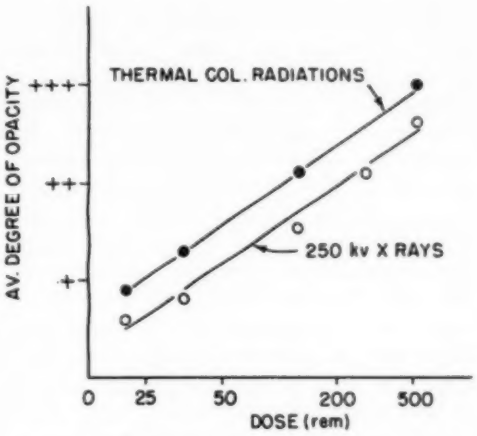

Fig. 7. Opacities in RF mice sixteen months after exposure to 250-kvp x-rays or to thermal column radiations (the latter were contaminated by gamma rays, thermal neutrons constituting less than one-third the total dose in rep). Doses are expressed in rem based on 30-day x-ray lethality.

COMMENTS

High Relative Effectiveness of Neutrons: The high RBE of neutrons for lens injury noted in each of these experiments is in agreement with earlier observations (Evans, 1948; Christenberry and Furth, 1951; Cogan *et al.*, 1952; Storer and Harris, 1952; Leinfelder *et al.*, 1955). It is noteworthy that, for all the species studied, the relative cataractogenic effectiveness of cyclotron neutrons was essentially the same, that it was identical to that of fission neutrons liberated by nuclear detonation, within the experimental error of the methods employed, and that the RBE of thermal neutrons approximated the same value.

The even higher RBE observed for Po-B neutrons (Fig. 6), which is in agreement with the figure of 9 to 11 obtained by Cogan *et al.* (1952) for 14-MEV or 300-kev neutrons in rabbits and with the value of 8 reported by Leinfelder *et al.* (1955) for 4-MEV neutrons in mice, may have resulted from the use of doses which were lower than those of the other types of neutrons, the higher RBE being based therefore on opacities of a milder degree. There is some evidence that the RBE of neutrons may be appreciably higher for the production of threshold lens injury than for the causation of mature cataracts, as pointed out by Ham (1953); this is suggested by the data of the Po-B experiment, the RBE increasing above 9 at the lower dose levels and by the results observed in the experiments with cyclotron neutrons (Fig. 4) and fission neutrons (Fig. 5). This type of variation of the RBE of neutrons as a function of the dose is characteristic for chromosomal exchanges, as observed in *Tradescantia* (Lea, 1947), the effect being linear with the dose of neutrons and independent of the intensity of neutron irradiation, but proportional to the square of the dose of x-rays and the intensity of x-irradiation. It is conceivable that this type of injury is the primary mechanism of cellular damage in irradiation cataractogenesis.

The elevation of the RBE of Po-B neutrons may also have been based in part on the lower dose rate of radiation employed, since the relative effectiveness of neutrons, as compared with x-rays has been observed to be greater for chronic than for acute exposures in causing various types of injury (Henshaw *et al.*, 1947; Evans, 1948; Stone, 1948). No significant change in the RBE for lens opacification was observed in the present experiment on fractionation of the dose, however; and the rate dependence of the RBE may not be as significant for lens damage as for injury of other types, from which there may be more rapid recovery.

Another factor which might conceivably account for some of the observed differences in the RBE is variation in the neutron energy. Leinfelder *et al.* (1955) and Riley *et al.* (1955) have reported that the RBE of fast neutrons decreases with increasing energy over the range of 1 to 7 MEV. However, Cogan *et al.* (1952) observed no significant difference in cataractogenic effectiveness between neutrons of a modified fission spectrum (peak energy 300 kev) and 14-MEV mean energies. Furthermore, the neutron/x-ray effectiveness ratio has been observed by others to be fairly constant (1.5–1.7) over the energy spectrum from thermal to 14-MEV energies for acute lethality and thymus weight loss in mice (Brennan *et al.*, 1954; Harris and Ellinwood, 1953; Carter *et al.*, 1954; Upton *et al.*, 1956). As regards cataract induction, the uniformity of the RBE for lens opacities observed in the present experiments with cyclotron, fission, and thermal neutrons suggests that at the lower end of the spectrum there is no significant variation of the neutron RBE with energy. It is noteworthy in this connection that von Sallmann *et al.* (1955) have observed 380-MEV alpha particles and 190-MEV deuterons to be approximately four times as effective as 200-kv x-rays in causing cytologic damage to the anterior epithelium of the rabbit lens.

Relative Effectiveness of X and Gamma Rays: In the LAF_1 and RF mice irradiated at high dose levels and at high intensities, 250-kvp x-rays appeared to be slightly more cataractogenic than gamma rays (RBE approximately 1.2). These observations are consistent with those of Clark and Sykowski (1952), who noted a more rapid onset and progression of opacities in CF1 mice exposed to 124-kvp x-rays than in those irradiated with 50-MEV x-rays from a betatron, although they did not consider the difference to be significant. For most biological effects in mammals, the RBE of the photon has been found to vary in proportion to the wave length (Zirkle, 1954). The failure to observe a detectable difference in cataractogenic effectiveness between 250-kvp x-rays and Co^{60} gamma rays at low dose levels and with low dose rates (Po-B experiments) is probably attributable to the reduction in the sensitivity of the biological index (opacification of the lens) which is encountered as threshold dose levels are approached.

Cataractogenic Threshold Dose: From these experiments, it is evident that the radiation tolerance of the lens differs with species and also with the type of ionizing radiation administered. The mouse exhibits detectable opacities in response to doses as low as 15 to 30 r of x-rays or 1 rep of fast neutrons (Po-B), whereas similar threshold changes require considerably larger doses in the rat and still greater amounts of radiation in the rabbit. From the evidence now available, the human lens appears to be considerably more radioresistant than that of the small laboratory mammals (Table II). McDonald *et al.* (1955) concluded from study of beta-ray cataracts that the lens of the rabbit was approximately four times as radiosensitive as the human lens, the threshold dose for cataract formation being approximately 60 to 120 rep in the rabbit and 200 to 1,200 rep in man. The latter estimate closely approximates the figures given by Merriam (1955) for similar beta-ray-induced opacities in the human lens.

The values reported in the literature

TABLE II: RELATIVE EFFECTIVENESS OF DIFFERENT IONIZING RADIATIONS IN CATARACT FORMATION

Species	Radiation	Dose rate†	Threshold cataracto-genic dose (rep)*	Latent period	RBE	Reference
Man	X-ray (200 kv)	b	600	2 yr	..	Cogan and Dreisler, 1953
	X-ray (130 kv)	..	875	5 yr	..	Hunt, 1947
	X-ray (130 kv)	..	1,350	5 yr	..	Hunt, 1947
	X-ray (200 kv)	b	1,400	1½–2 yr	..	Leinfelder and Kerr, 1936
	Beta ray	c	1,600	4 yr	..	Haik *et al.*, 1954
	Beta ray	d	200–1,200	3 yr	..	McDonald *et al.*, 1955
	Beta ray	c	230–1,120	3–6½ yr	..	Merriam, 1955
	Fast neutron (0.3 MEV)	e	15–45	3–5 yr	..	Ham, 1953
	Fast neutron (<10 MEV)	f	20–150	3 yr	..	Abelson and Kruger, 1949
	Fast neutron (<10 MEV)	f	20–150	3 yr	..	Krause and Bond, 1951
Rabbit	X-ray (1.2 MEV)	d	500‡	4 mo	1	Cogan and Donaldson, 1951
	Fast neutron (0.3 MEV)	d	54‡	4 mo	9	Cogan *et al.*, 1952
	Fast neutron (14 MEV)	d	45	4 mo	11	Cogan *et al.*, 1953
	X-ray (200 kv)	d	600	4 mo	..	Leinfelder and Kerr, 1936
	Beta ray	d	750	3 mo	..	von Sallmann *et al.*, 1953
	Beta ray	d	60–120	4–5 mo	..	McDonald *et al.*, 1955
	Fast neutron (6–8 MEV)	d	80–250	2–5 mo	..	Moses *et al.*, 1953
Mouse	X-ray (185 kv)	f	...	....	1	Evans, 1948
	Fast neutron (<10 MEV)	f	...	....	>4§	Evans, 1952
	X-ray	d	...	....	1	Leinfelder *et al.*, 1955
	Fast neutron	d	...	....	8	
	Fast neutron (4 MEV)	b	...	....	8	
	Fast neutron (<4 MEV)	d	...	....	5	
	Fast neutron (<4 MEV)	b	...	....	8	
	X-ray (250 kv)	d	4	4 mo	1	Storer and Harris, 1952
	Slow neutron	d	50	4 mo	6	Harris, 1954
	X-ray (250 kv)	d	32	6 mo	1	Christenberry and Furth, 1951
	Slow neutron	d	20	6 mo	>1	Upton *et al.*, 1954
	X-ray (124 kv)	d	....	....	1	Clark and Sykowski, 1952
	X-ray (50 MEV)	d	...	....	>1	
Dog	Fast neutron (6–8 MEV)	d	2,000	17 mo	..	Moses *et al.*, 1953

* Doses reported in n units or roentgens were converted arbitrarily to rep by the formulas 1 r = 2.5 rep and 1 r = 1 rep.

† b. Fractionated daily exposures. c. Intermittent exposure of variable total duration. d. Single exposure of short duration. e. Accidental nuclear detonation, with instantaneous exposure. f. Chronic exposure.

‡ Cogan *et al.* (1952) reported the development of detectable opacities in rabbits exposed to 75 r of x-rays or 1 rep of neutrons; however, these opacities were not observed to progress beyond a mild stage and were not severe enough to significantly impair vision.

§ Evans has estimated that the RBE of neutrons administered to his mice in repeated exposures over a long period might have been as high as 34.

(Table II) indicate that the cataractogenic dose for man is probably in the neighborhood of 600 to 1,400 rep of x-radiation, and less than 150 rep of neutrons; attempts to estimate the threshold dose for neutron radiation in man, however, are complicated by many uncertainties, one of which is the lack of reliable neutron dosimetry in the human cases observed thus far (Ham, 1953). Another difficulty arises from the absence of information about the recuperative capacity of the lens. Thus it is not known whether the threshold dose for damage is appreciably higher for chronic irradiation administered at low dose rates than for exposures at high intensities. Although the observations reported herein suggest that there is slight recovery between fractionated doses of either neutrons or

gamma rays in mice, more quantitative data and observations in other species are needed.

Since the values for RBE now available are based primarily on experiments with single-dose irradiation, it is not advisable to extrapolate from these data in estimating the maximum permissible exposure level for chronic neutron irradiation of the lens. The relative neutron effectiveness may conceivably increase with reduction of the dose rate, as suggested earlier.

Mechanism of Cataractogenesis: The pathogenesis of radiation cataract has been reviewed by Ham (1953). It would appear from the evidence available that the opacification stems directly or indirectly from irradiation injury of cells of the anterior lens epithelium: however, the relation between epithelial injury and the occurrence and severity of degenerative changes of cortical fibers is not clear (Friedenwald and Rytel, 1955).

Although the mechanism is not yet understood, the high RBE of neutrons may result from the relative inability of the lens to get rid of damaged cells or fibers owing to its surrounding capsule and avascularity, as suggested by Evans (1952), since neutrons and other densely ionizing radiations have been found to be highly effective in killing mammalian cells in tissue culture or transplantation (Zirkle, 1954).

SUMMARY

For the production of cataracts in mice, rats, and guinea-pigs, cyclotron neutrons of 1 to 2 MEV mean effective energy, administered at high intensity, were two to four times as effective as 250-kvp x-rays and three to four times as effective as 1.2-MEV gamma rays; fission neutrons from an experimental nuclear detonation and thermal neutrons had a similar cataractogenic effectiveness in mice.

The radiosensitivity of the lens varied appreciably with species; the mouse, rat, guinea-pig, and rabbit exhibiting decreasing sensitivity in the order listed, all being presumably more sensitive than man.

With fractionation of neutron or gamma irradiation, there appeared to be only slight, if any, reduction in dose effectiveness at low dose levels in mice.

The RBE of fast neutrons of 2 to 3 MEV mean energy (Po-B) administered at relatively low intensities was approximately 9 for induction of mild opacities in mice and appeared to be greater than 9 for the production of threshold lens damage, the relative cataractogenic effectiveness of these and of the other fast neutrons varying inversely with the dose and with the severity of lens injury.

ACKNOWLEDGMENT: The authors are grateful to Mrs. E. S. Ledford and Mr. J. R. Thomson, Jr., for technical assistance. It is also a pleasure to thank Dr. C. W. Sheppard for technical advice and consultation, and to acknowledge the assistance of Messrs. J. J. Lane, F. P. Conte, and J. L. Nelson in dosimetry and in the irradiation of the animals.

Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tenn.

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SUMARIO

La Relativa Eficacia Biológica de los Neutrones, los Rayos X y los Rayos Gamma para la Producción de Opacidades del Cristalino: Observaciones en Ratones, Ratas, Cobayos y Conejos

Estos experimentos se proponían obtener información cuantitativa acerca de la relativa eficacia biológica (REB) de los neutrones, rayos X y rayos gamma para la producción de opacidades del cristalino en varias especies de mamíferos pequeños. En ratones, ratas y cobayos, neutrones de ciclotrón de 1 a 2 MEV de energía eficaz media, administrados a alta intensidad, resultaron ser de dos a cuatro veces más eficaces que los rayos X de 250 kv y de tres a cinco veces más eficaces que rayos gamma de 1.2 MEV. Neutrones fisionados procedentes de una detonación nuclear experimental y neutrones térmicos mostraron una eficacia cataratógena semejante en los ratones.

La radiosensibilidad del cristalino varió apreciablemente según la especie, manifestando el ratón, la rata, el cobayo y el conejo sensibilidad decreciente en el orden enumerado, y siendo todos presuntamente más sensibles que el hombre.

Al fraccionarse la irradiación con neutrones o gamma, no pareció haber más que una reducción leve, sino nula, en la

eficacia a cifras bajas de dosis en los ratones.

La REB de los neutrones veloces de 2 a 3 MEV de energía media (procedentes de un foco de Po-b), administrados a intensidades relativamente bajas fué aproximadamente de 9 para la inducción de opacidades leves en los ratones y pareció ser superior a 9 para la producción de lesión umbral en el cristalino, variando la relativa eficacia cataratógena de estos y otros neutrones veloces en razón inversa a la dosis y la gravedad de la lesión del cristalino.

DISCUSSION

Howard H. Vogel, Jr., Ph.D. (Lemont, Ill.): In some exposures to fission neutrons at Argonne we found that we could not give a single whole-body dose of gamma rays to CF1 female mice that would produce what Dr. Upton calls a Type 4 cataract in a relatively short time and still keep the animal alive. Therefore, we tried protecting the animals with cysteine (injected prior to irradiation) and found that they would stay alive long enough for cataracts to develop. One can produce a Type 4 cataract with single doses on the order of 1,000 to 1,200 r of Co^{60} gamma rays. However, it takes a minimum dose of only about 150 rep of fission neutrons to produce the same effect. Therefore, at least with our strain of mice, exposed in our radiation chamber, the RBE to produce the end-result, namely, complete opacity of the lens within one year, was on the order of 6 or 7 rather than the 3 reported by Dr. Upton.

The Effects of Conventional and High-Energy X-Rays and Electrons in Fractionated Dosage on Rats[1]

WALTER S. MOOS, Ph.D., JOHN B. FULLER, M.D., WALTER J. HENDERSON, and ROGER A. HARVEY, M.D.

THE USE of very high-energy gamma and electron radiation for the treatment of cancer in man poses the question of the eventual biological effects on the tissues involved. Does radiation of such type cause a different response qualitatively and/or quantitatively in comparison to standard x-ray exposure? Investigation of this problem is a prerequisite to the application of high-energy radiation therapy. Though many studies have been conducted (1–6), research is continued in the interest of improving treatment technic and enhancing the response of the malignant tissues to radiation.

Biological effectiveness has been observed to vary with the energy of the irradiating agent (7–9, and others). Quastler (5), Haas (1), and others have demonstrated such variation in biological objects irradiated with betatron x-rays of 22 MEV and electrons of similar energy. The difference of the effects as compared with those of 400- and 200-kv x-ray exposures seems to be of an entirely quantitative nature; no qualitative changes could be detected.[2]

The purpose of the experiments to be recorded here was to establish the degree to which fractionated x-ray and electron dosages influence the survival and other biological activities of rats in comparison to equal amounts of ionizing radiation of lower energy.

METHODS

For these experiments, male albino rats of the Holtzman strain were used. A two-week period was allowed for conditioning the animals to their new environment before the first irradiation took place.

The rats were sorted at random into several groups, each consisting of 22 animals. One group was used for exposure to 400-kv x-rays generated by a General Electric 400-kv unit (h.v.l., 2.1 mm. Cu). A second group was irradiated by a 22-MEV betatron x-ray source (h.v.l., 14 mm. Pb), while a third received electron radiation of 20 MEV energy.[3] A final group was kept as a control but, except for exposure to radiation, was handled exactly as were the other animals.

From each group 11 rats were treated simultaneously in a rotating Lucite cage, described elsewhere (11). This allowed more uniform irradiation and reduced errors due to individual dosage variations to a minimum. It also resulted in a saving of time since the wheel was placed at such a distance from the radiation source that only 6 r/min. were delivered to the animals. In this location the entire rotating cage (1 rpm) was uniformly covered by the 400-kv and 22-MEV x-ray beams. For electron beam irradiation, only sectional areas of the wheel could be irradiated. The electron beam was defined by a Lucite and brass shield having an opening identical in configuration with each of the twelve individual compartments in the Lucite wheel. Instead of aligning the axis of rotation with the center of the beam, as was done in the case of x-rays, the wheel was so set up that the pie-shaped electron beam bombarded only one entire animal as it passed by during the rotation. In contrast to the other experiments, precise

[1] From the Departments of Radiology and Pathology, College of Medicine, University of Illinois, Chicago. This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service. Accepted for publication in December 1955.

[2] This seems to be true for large animals, but not always for single cells. Lindenmann (10) and Laughlin (personal communication) have shown little or no variation in the effects on bacteria irradiated with 200-kv and 22- or 31-MEV x-rays. This is in accordance with the author's findings (7).

[3] A 400-kv and a control series were run parallel with each group of animals exposed to other energies.

TABLE I: MEAN SURVIVAL TIME AND RBE FACTOR FOR RATS IRRADIATED WITH 400-KV X-RAYS AND 22-MEV X-RAYS AND ELECTRONS

r/day	X-rays 400 kv (days)	X-rays 22 MEV (days)	Electrons 20 MEV (days)	RBE (from 50% survival)	Experiment
150	15.4	...	20.4	0.69	I
100	24.8	...	42.8	0.51	II
50	68.0	122.0	..	0.57	III
150/250	11.8	11.6	..	1.09	IV
150/250	16.2	...	16.2	1.06	V

daily dose applied to the animals. Figure 1 shows the results obtained with 400-kv x-rays delivering dosages of 50, 100, and 150 r/day. The abscissa represents the days after irradiation was begun and the ordinate indicates the per cent survival. The data obtained with 22-MEV x-rays (50 r/day) and the 20-MEV electron beam (100 and 150 r/day) are plotted on the same graph. The slope of the curves for the 150-r/day groups are closely similar.

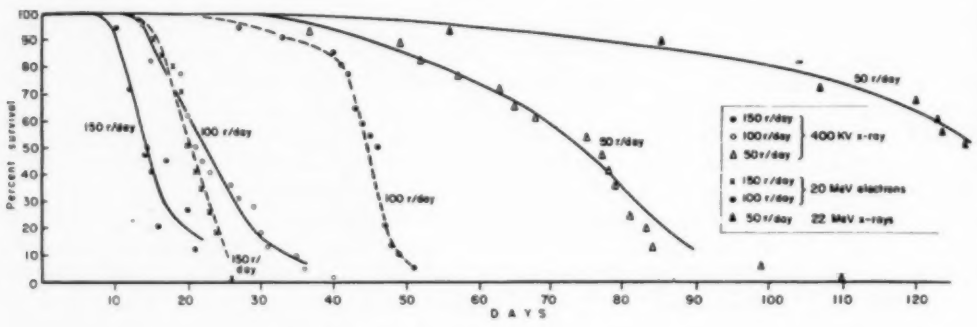


Fig. 1. Survival curves for rats irradiated with 400-kv x-rays, 22-MEV x-rays, and 20-MEV electrons.

timing of the beginning and termination of radiation and rotation was necessary in this instance, in order to assure that all animals passed through the beam an equal number of times and received the same dose.

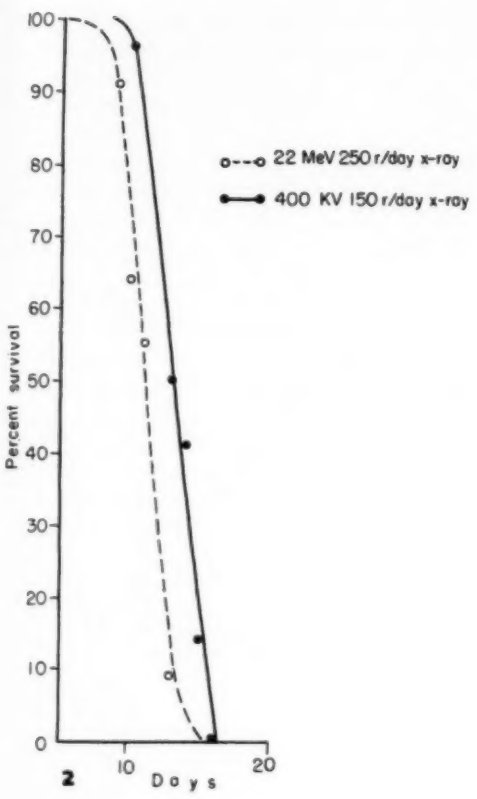
For proper 22-MEV x-ray dose distribution within the animal, one is compelled to place 2.5 cm. die stock (equal to 4 cm. water) between the rats and the beam. This causes maximum ionization build-up at the position where the animals are treated. Such provisions are not necessary, however, if 400-kv x-rays or electrons are used. Each run was monitored with a 100-r Victoreen ionization chamber placed in the twelfth compartment of the wheel. This was done after the dose distribution in the animals was established by Victoreen and film measurements in phantoms prior to the experiment.

RESULTS AND DISCUSSION

Survival Studies: A comparison was made of the survival times in relation to the

In the experiments employing 100 r/day, however, the 400-kv curve regresses more slowly than that for the electron beam. In contrast to this, for the 50-r/day animals, the 400-kv curve falls off more steeply than that for the betatron x-rays. We are not in a position at the present time to decide if this discrepancy is due to an experimental error or is of any real significance. The mean survival time and the RBE (based on 50 per cent survival) for 400-kv and high-energy irradiation are set forth in Table I.

Since these experiments were carried out by giving the low- and high-energy groups the same physically determined dose, one could question whether or not recovery and other biological factors might be differently influenced if the relative biological effectiveness of the various radiations were not comparable. In answer to this problem, a group of animals was irradiated with 400-kv x-rays and another group with betatron x-rays. The daily dosage, however, was 150 r/day for the low-energy and 250 r/day for the high-energy rays



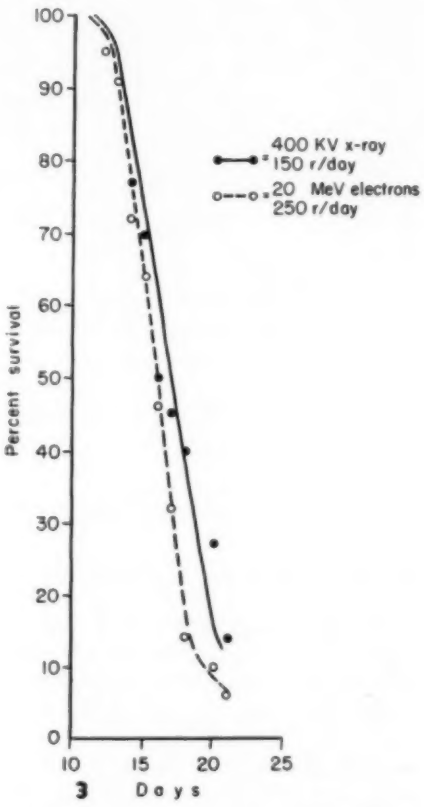


Fig. 2. Survival curves for rats irradiated with 22-MEV x-rays in doses of 250 r/day and with 400-kv x-rays in doses of 150 r/day.

Fig. 3. Survival curves for rats irradiated with 20-MEV electrons in doses of 250 r/day and 400-kv x-rays in doses of 150 r/day.

(Fig. 2). The ratio of the two dose rates

$$\frac{150 \text{ r/day}}{250 \text{ r/day}} = 0.6$$

corresponds approximately to the average RBE values obtained in the previous experiments. The increased dose rate of the betatron radiation resulted in a survival pattern which is almost identical with the 400-kv x-ray curve obtained with 150 r/day. The betatron animals died at a somewhat faster rate in this experiment, causing a difference of 15 per cent between the survival curves, which are otherwise identical. A dose ratio of $\frac{150 \text{ r/day}}{212 \text{ r/day}} = 0.7$ would actually be called for in order for the two curves to be superimposed. Values of about 0.7 have been found previously in single-exposure experiments on various biological material. The 50 per cent survival time ratio indicates practically no difference (see Table I, Exp. IV, RBE 1.09). Electron-beam irradiation for an equivalent of 250 r/day in comparison to 150 r/day with 400-kv x-rays gave similar results (Fig. 3). Again the animals died a little earlier if bombarded with the high-energy particles, causing a divergence of the two curves ranging from 2 to 8 per cent. Nevertheless, in this experiment also, the comparison of both 50 per cent survival time values showed almost unity for the RBE factor.

These observations make it appear as if

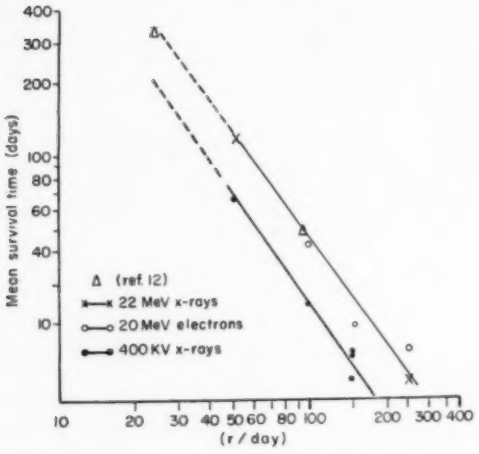


Fig. 4. Linear curves obtained by plotting the common log of dose rate vs. the common log of survival time.

the RBE value remains constant whether the dose rates are the same for both groups or the high-energy dosage is increased.

Rust *et al.* (12) claim that if one plots the common log of the dose rate (r/day) versus the common log of survival time (days) of Co^{60}-irradiated burros, a linear graph is obtained. The data from our experiments produced similar curves (Fig. 4). The lines obey the following equations:

400-kv x-rays: $\log y = -1.45 \log x + 4.3$ (1)

and

22 MEV x-rays and 20 MEV electrons:

$$\log y = -1.45 \log x + 4.56 \quad (2)$$

where y represents the mean survival time in days and x the dose rate (r/day). Values given by Thomson *et al.* (13) for rats exposed to 25–30 r/day and 90–100 r/day Co^{60} radiation fit very closely to the curve drawn through our experimental points by the mean square method. A comparison of curves obtained from Rust's and Thomson's data show considerable difference between the response of rodents (mice and rats) and burros, as well as guinea-pigs. It is of interest that there seems to be no energy dependence observable between the radiation effects of Co^{60} and betatron sources.

Equations 1 and 2 are probably correct only in a range of 25 r/day to 250 r/day, since at zero exposure ($x = 0$) they would indicate a mean survival time for rats of 2×10^5 to 3.6×10^5 days. This is impossible and suggests a smaller slope at smaller daily radiation dosages, as is also

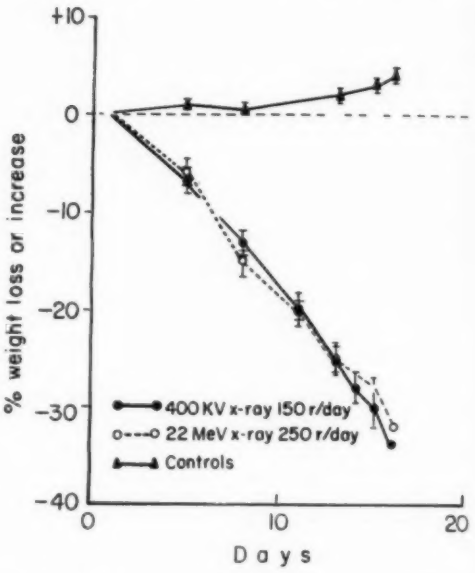


Fig. 5. Weight-loss curves for 400-kv x-rays (150 r/day), 22-MEV x-rays (250 r/day), and controls.

indicated by the observations of Lorenz and co-workers on mice, etc. (14, 15).

Weight Response: It is known that the loss of body weight is one of the symptoms of injury produced by ionizing radiation. The effects of single and repeated exposures on animal weights have been the subject of numerous investigations (16, 17).

During our survival experiments, the animals were weighed once or twice a week and records of loss or gain were kept. The weight of the animals at the time of arrival was approximately 400 gm.

The period of measurements for the 150-r/day (400-kv x-rays and 20-MEV electrons) group was relatively short and therefore the curves are based on few points. There is no doubt, however, that, with the exception of the first eight days after irradiation was begun, the weight

loss of the x-ray-irradiated animals had an increased pace compared to the electron beam group.

The application of 100 r/day of 400-kv x-rays and of 20-MEV electrons caused an identical initial weight drop for ten to eleven days, after which the loss became less marked in the animals treated with the electron beam, whereas in the 400-kv group it showed only an insignificant slowing down until death occurred. In the betatron-irradiated group weight reduction remained almost stationary from the eleventh to the thirty-sixth day, after which there was a more rapid decrease until the end. The phenomenon of initial identical weight loss following irradiation at 400 kv and 22 MEV was observed, too, at a dose rate of 50 r/day. Here, after

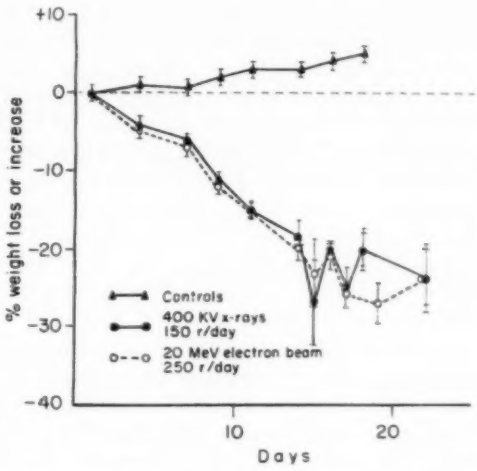


Fig. 6. Weight-loss curves for 400-kv x-rays (150 r/day), 20-MEV electrons (250 r/day), and controls.

TABLE II: ABNORMALITIES IN RATS IRRADIATED WITH 400-KV AND 22-MEV X-RAYS OR 20-MEV ELECTRONS IN FRACTIONATED DOSAGE

Radiation type, energy, and dose rate	No. of animals	External bleeding	Thymus	Lungs	Spleen	Stomach	Intestine	Liver	Kidneys	Brain	Testes	Lymph nodes	Heart and pericardium
400-kv x-rays 150 r/day	22	14%	68%	68%	77%	77%	82%	...	9%	5%	82%	23%	9%
400-kv x-rays 100 r/day	20	55%	5%	65%	70%	85%	50%	...	...	...	55%	40%	15%
400-kv x-rays 50 r/day	17	6%	...	88%	6%	...	...	...	...	...	...	...	...
20-MEV electrons 150 r/day	18	17%	50%	72%	89%	95%	67%	...	...	...	78%	30%	28%
20-MEV electrons 100 r/day	22	73%	91%	59%	95%	87%	32%	...	...	...	73%	...	5%
22-MEV x-rays 50 r/day	18	...	73%	...	...	...	...	...	...	...	...	...	...

approximately five days the curves showed a certain maintenance of weight (12, 13, 18–20)—or rather weight loss was balanced by recovery over the weekends—for about thirty-five days before this changing pattern became less pronounced.

A second period of weight reduction started about fifty-eight days after the first treatment with 400-kv x-rays. From this time on the animals showed a continuous weight decline. A far less dramatic weight change occurred in the betatron series, but this did not begin before about the seventy-fifth day.

The weight curves plotted in Figs. 5 and 6 are the results of exposures (Exps. IV and V, Table I) to 150 r per day of 400-kv x-rays and 250 r per day of 22-MEV x-rays or 20-MEV electrons. Both are evidence that the mechanism of the radiation energy-weight loss relationship is qualitatively of the same nature for low energy x-rays and highly penetrating radiation with the exception of a quantitative constant, namely, the RBE factor.

Pathological Examination: A summary of the pathological changes observed is presented in Table II. Thymus and

spleen almost without exception were about one-fifth normal size—the latter soft and sometimes black—as was to be expected for radiosensitive organs. Also the lungs were strongly affected in all groups and at all dose rates. Congestion, atelectasis, and petechiae were common findings in most autopsies, as were blood-distended stomachs and intestines. Practically no abnormalities were found in the liver, kidneys, and brain (21) which could be attributed to radiation damage. The testes were frequently observed to be atrophic, congested, and with occasional scrotal bleeding. Lymph nodes showed signs of hemorrhage and were often small, dark red, and soft. In many instances superficial bleeding occurred, as in the mouth, nose, and eyes. Not many cases of congestion, hemorrhages and petechiae of the cardiac system were found.

SUMMARY

1. Survival studies on rats irradiated with fractionated dosages of 400-kv and 22-MEV x-rays revealed no qualitatively different reaction.

2. The relative biological effectiveness of the two energies of ionizing radiation was of the order of 0.56 to 0.75. The lower RBE factor at smaller daily dosages (50 and 100 r/day) is in accordance with similar findings by Quastler and Lanzl (22), who irradiated mice with divided doses of betatron x-rays.

3. Irradiation of rats with 20-MEV electrons produced results almost identical with those obtained with 22-MEV x-rays. The RBE value also remained unchanged.

4. No significant variation of the RBE value was obtained by treating the animals at a

$$\frac{150 \text{ r/day (400-kv x-rays)}}{250 \text{ r/day (22 MEV x-rays or 20 MEV electrons)}} = 0.6$$

or at 1:1 dosage ratio.

5. Weight loss variations can also be attributed only to a quantitatively different process. Again the RBE factor approximates closely a 0.6–0.7 value.

6. Gross pathological examination gave no clues suggesting any other damages than those generally observed in mammals exposed to low-energy x-rays.

840 S. Wood St.
Chicago 12, Ill.

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SUMARIO

Los Efectos de los Rayos X y los Electrones Convencionales y de Alta Energía a Dosis Fraccionadas sobre las Ratas

Estos experimentos tenían por mira establecer los efectos biológicos de la irradiación fraccionada con rayos X y electrones sobre las ratas, en comparación con cantidades iguales de radiación yonizante de menor energía (400 kv).

Los tiempos de sobrevivencia para los animales irradiados con rayos X de 22-MEV no discreparon cualitativamente de los consecutivos a la irradiación de 400 kv. La relativa eficacia biológica (REB) de las dos energías de radiación correspondió al orden de 0.56 a 0.75. La irradiación con electrones de 20 MEV produjo resultados casi idénticos a los obtenidos con rayos X de 22 MEV.

La alteración de la proporción de las dosis de las radiaciones de energías alta y baja no produjo mayor variación en su REB.

Los efectos sobre la pérdida de peso, los mismo que los efectos sobre la sobrevivencia, fueron puramente cualitativos.

En los animales de experimentación no se observaron más alteraciones histopatológicas que las atribuibles ordinariamente a las radiaciones de baja energía.

Roentgen Changes Following Radical Neck Dissection[1]

S. AARON SIMPSON, M.D., SEWELL S. GORDON, M.D., JOSEPH JORGENS, M.D., and LEO G. RIGLER, M.D

WE PROPOSE TO describe and demonstrate the changes in the posteroanterior roentgenograms of the chest resulting from a relatively common surgical procedure, the radical neck dissection described by Crile. This problem first presented itself when we noted in one of our cases (Case 1) a calcific excrescence on the clavicle, the significance of which was not understood until we learned that the patient had been subjected to a radical neck dissection. We concluded that the calcific projection represented a spur consequent to surgical trauma to the clavicular periosteum. Subsequently we collected and analyzed all available cases of neck dissection performed in this hospital and observed other roentgenographic stigmata referable to the operation.

It is well known that many surgical procedures are associated with characteristic roentgenographic manifestations and can thus be recognized by the radiologist with a high index of assurance, even in the absence of a clear history. Radical mastectomy provides the outstanding example of an operation which produces changes recognizable for what they are even in the absence of a history. Knowledge of previous surgery is often one of the important building blocks essential for correct interpretation of a roentgen study. Every roentgenologist is aware of the orientation of his thought processes following directly

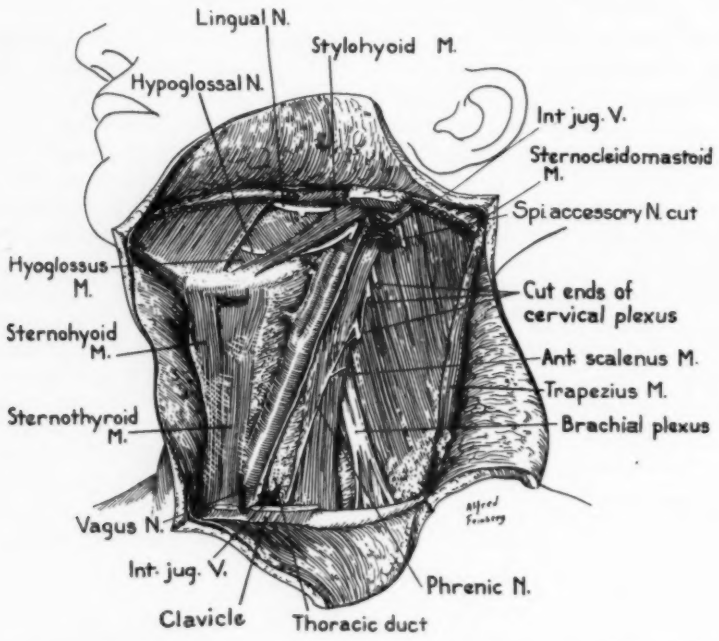

Fig. 1. Diagrammatic representation of completed neck dissection prior to closure. Note the exposure of the clavicle. This photograph is reproduced through the kind permission of Dr. Hayes Martin and *Cancer* (**4**: 467, Fig. 10, May 1951).

[1] From the Department of Radiology of the Veterans Administration Hospital and of the University of Minnesota, Minneapolis, Minn. Accepted for publication in January 1956.

upon observation of the absence of the breast shadow. In the same way, he may recognize the presence of a radical neck dissection by the roentgen findings, even without prior knowledge of the procedure.

The value of roentgenographic recognition of a previous surgical procedure may be threefold: (*a*) It may provide the radiologist, and even the clinician, with information which is not otherwise available to them. (*b*) Pursuant to the above, it will direct the radiologist's attention toward pathology of the type that may reasonably follow as a complication of the surgery or the underlying disease process. (*c*) It may assist the radiologist to avoid the pitfall of interpreting the changes resulting from surgery as a spontaneous pathologic process or an anatomic abnormality. Certainly, in most instances, this last consideration would be dominant.

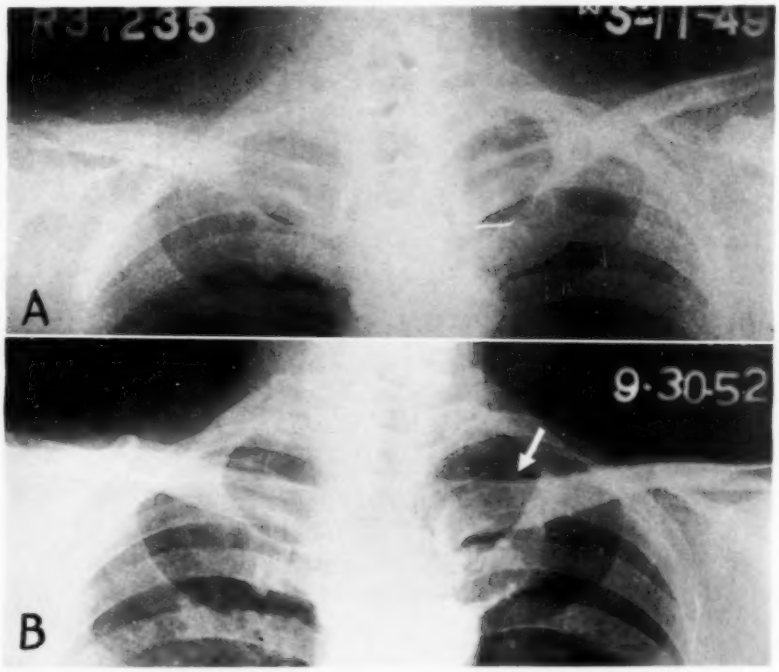

Fig. 2. Case I. A. Preoperative roentgenogram of apices. B. Roentgenogram following left radical neck dissection, showing spur on clavicle (arrow), apical radiolucency, loss of sternomastoid muscle shadow, and regional soft-tissue defect. Note the shadow of the skin reflection above the clavicle on the normal right side and its abrupt termination laterally at the level of the scapula.

THE SURGICAL PROCEDURE

The radical neck dissection done in the cases reported here conforms essentially to the procedure described by Crile. The accompanying diagram (Fig. 1) illustrates the appearance of the completed dissection prior to skin closure.

The side operated upon presents salient anatomical features, important from a radiographic standpoint, as follows:

1. General soft-tissue deficiency.
2. Absence of the sternomastoid muscle.
3. Interruption of the eleventh cranial nerve, innervating the trapezius muscle. The nerve is frequently excised, although occasionally left intact.
4. Abnormalities of the clavicle resulting from surgical trauma, since the upper border provides the inferior margin of the dissection field. This may promote a visible periosteal reaction taking the

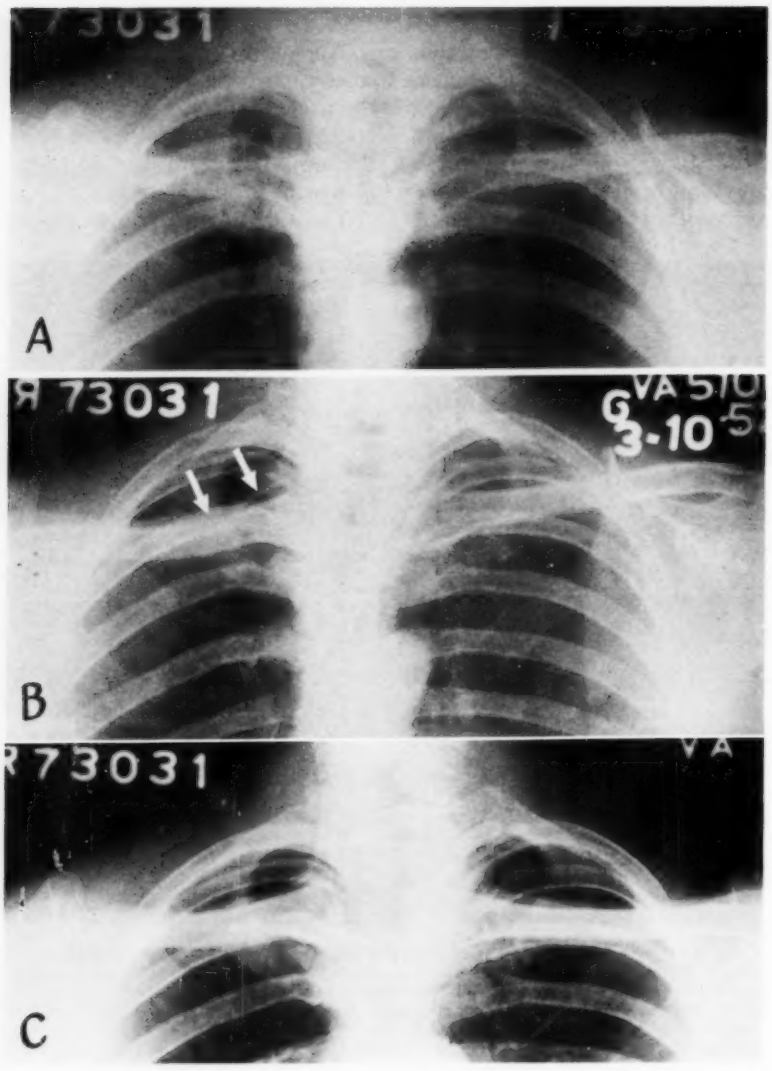

Fig. 3. Case II. A. Preoperative. Normal skin reflection shadow well shown on both sides. B. Roentgenogram following right radical neck dissection. Periosteal reaction on superior surface of right clavicle is particularly marked medially (arrows) but extends laterally right up to the acromioclavicular joint, distinguishing it from the usual skin reflection. There are also apical radiolucency, regional soft-tissue deficiency, loss of the sternomastoid muscle shadow, and shoulder drop with scapular rotation. C. Roentgenogram after second neck dissection, this time on left side. All the changes previously described on the right are now seen on the left.

form of subperiosteal calcification or ossification.

5. Injury or destruction, generally inadvertent, to the phrenic nerve, which courses downward in a vulnerable position on the floor of the dissected region. When this occurs, partial or complete paralysis of the diaphragm may result.

In contradistinction to the radical procedure, suprahyoid or upper neck dissection entails merely the removal of the contents of the submaxillary and submental

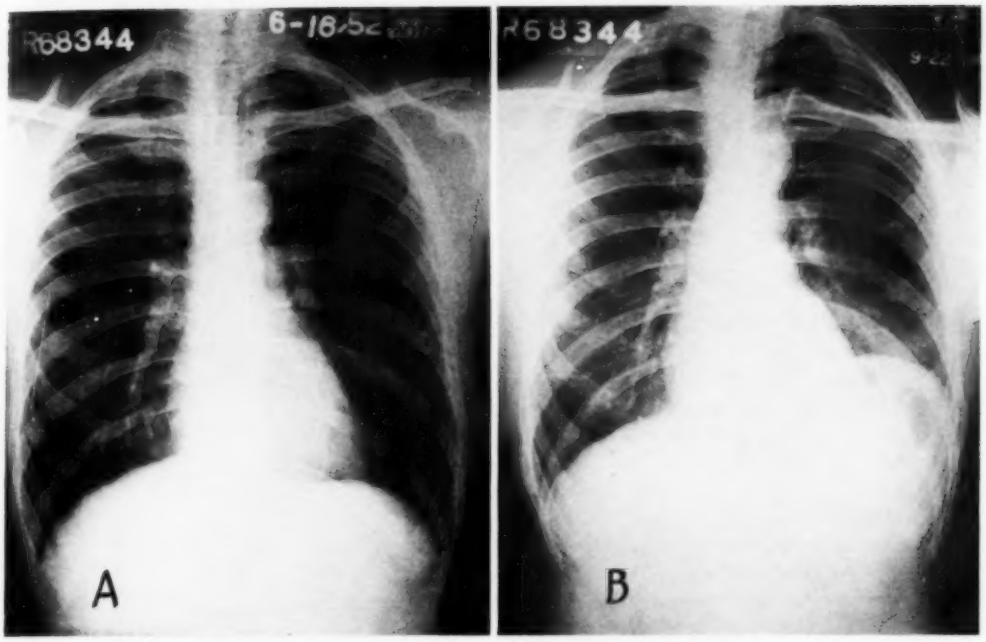

Fig. 4. Case III. A. Preoperative roentgenogram of chest. B. Roentgenogram after radical neck dissection on left side. Shoulder drop is particularly well shown, as are absence of the sternomastoid muscle shadow, regional soft-tissue deficiency, and increased radiolucency of the apex. There is no evidence of periosteal reaction. Note the elevated left diaphragm, indicating paralysis, no doubt from phrenic nerve injury.

triangles. Both the sternomastoid muscle and the eleventh cranial nerve are spared.

ANALYSIS OF CASES

Fifty-five consecutive cases of neck dissection were analyzed. Of these, 7 unilateral or bilateral suprahyoid dissections and 4 abortive, superficial, or modified dissections were eliminated from consideration. In none of these 11 were there any perceptible alterations in the roentgenograms. Also discarded were an extensive dissection including partial clavicular resection, in which the defect was so striking that no problem of recognition existed, and 10 cases of radical neck dissection in which postoperative films were unavailable. This left 31 unilateral and 2 bilateral radical neck dissections suitable for evaluation.

CASE REPORTS

CASE 1: A 54-year-old white male had a hemiglossectomy and left radical neck dissection for carcinoma of the tongue on May 26, 1949. The postoperative roentgenogram (Fig. 2) displays a clavicular periosteal reaction manifest as a triangular bony process arising from the medial part of the upper border of the clavicle. Also present are relative lucency of the apex and loss of the sternomastoid shadow. The soft-tissue defect is present, but is discernible on the original film only by use of a bright light.

CASE II: A 53-year-old white male had a partial glossectomy on Jan. 19, 1951, for squamous carcinoma. There followed a right radical neck dissection on Feb. 26. A recurrence was noted on the left side, and a left radical neck dissection was performed on Dec. 29, 1952. The film taken after the first dissection (Fig. 3B) shows a right-sided clavicular periosteal reaction in the form of a dense calcific line running roughly parallel to the upper clavicular border. The shadow can be traced well out laterally toward the acromioclavicular joint. Other alterations include right shoulder drop with scapular rotation, rarefaction of the apex, loss of the sternomastoid muscle, and regional soft-tissue defect.

A roentgenogram made following left-sided surgery (Fig. 3C) exhibited these same changes. The superior clavicular shadow extends well out to the acromioclavicular joint and is thus distinguished from the normal skin reflection.

CASE III: A 52-year-old white male had a left Crile neck dissection on July 17, 1952, followed by

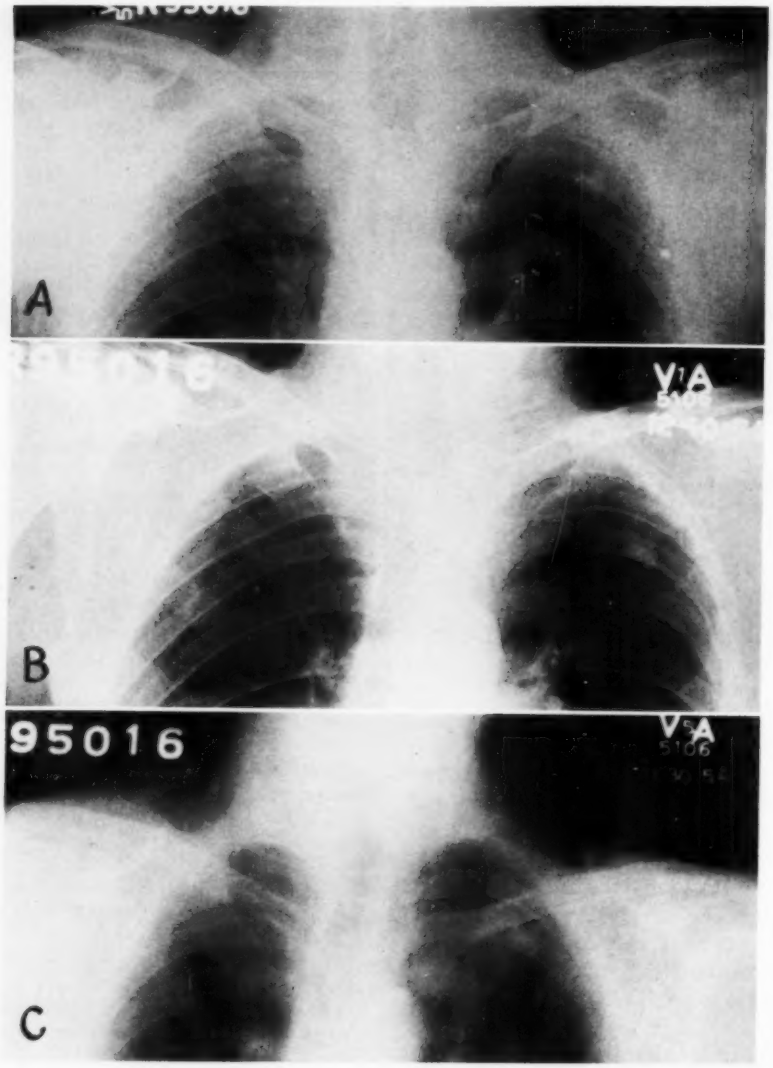

Fig. 5. Case IV. A. Preoperative. B. Postoperative 14 × 17-inch film, showing only absence of sternomastoid shadow on the left side. C. Postoperative miniature film, magnified to corresponding size, revealing other changes, including apical radiolucency, regional soft-tissue deficiency, and moderate shoulder drop. Calcification in the left upper lung is not pertinent.

radiation therapy to the neck for squamous carcinoma of the cervical nodes. A primary lesion had not been found at the time of this report, nor had there been a recurrence.

Postoperative alterations (Fig. 4) included apical lucency, shoulder drop with scapular rotation, loss of the sternomastoid shadow, and regional soft-tissue deficiency. In addition, there was a paralysis of the left hemidiaphragm.

CASE IV: A 59-year-old white male underwent excision of a carcinoma of the tongue and left buccal mucosa and a left radical neck dissection on Aug. 4, 1954. In December 1954 a cervical recurrence was noted and radiation therapy was given. The postoperative roentgenogram (Fig. 5B) shows only the absence of the sternomastoid shadow, and recognition of the neck dissection is well-nigh impossible. A miniature film, however, made a few days earlier

(Fig. 5C) reveals lucency of the apex, dropped shoulder, and a regional soft-tissue defect, thus making the dissection apparent.

RESULTS

Thirty-three cases were examined, with 35 areas affected, since in 2 instances the procedure was bilateral. Six more or less specific changes were noted. These are listed below with the number and percentage of the cases in which each change was manifested:

		Cases
1.	Loss of sternomastoid shadow	29 (83%)
2.	Increased radiability of the apex	25 (71%)
3.	Regional soft-tissue defect	24 (69%)
4.	Dropped shoulder	23 (66%)
5.	Clavicular periostitis	5 (14%)
6.	Diaphragmatic paralysis	4 (11%)

The number of changes resulting from each procedure varied, as is shown in the following tabulation.

No. of Changes	No. of Procedures
0	4 (12%)
1	2 (6%)
2	5 (14%)
3	5 (14%)
4	12 (34%)
5	7 (20%)
6	0 (0%)
	35

DISCUSSION OF RESULTS

Certainly the differences in the prevalence of the four commonest changes are not of statistical significance. Considering two of these commoner changes as the lower limit upon which to base a suspicion of abnormality, it would seem possible to suggest the diagnosis of radical neck dissection from the roentgenogram alone in approximately 80 per cent of the cases.

Of the alterations observed, loss of the sternomastoid muscle shadow is most frequent. This is one of the least striking of the alterations and must be specifically sought. When seen, it probably establishes the fact that dissection has been performed. Failure to observe this change may result from faulty positioning, as when most of the neck is not included on the roentgenogram.

A relative increase in radiability of the apex and a regional soft-tissue defect are manifestations of the same process, *viz.*, loss of soft-tissue mass and a consequent decrease of the thickness through which the x-rays must penetrate. A review of the original roentgen reports for this series revealed numerous cases in which the relative clarity of the apex on the affected side had been mistaken for emphysematous blebs; or the relative density of the contralateral apex was ascribed to pleural thickening or a vague infiltrate. What we have called "regional soft-tissue defect" is the more or less tangential projection of the narrowing of the soft-tissue mass above the apex at the junction of the neck and shoulder.

Dropping of the shoulder may be due in part to excision of the sternomastoid, but is primarily a consequence of destruction of the eleventh cranial nerve, innervating the trapezius muscle. If the nerve is spared, the shoulder sign will not occur. Also noted in this series, probably as a consequence of the loss of shoulder support, has been the development of osteoarthrosis of the sternoclavicular joint.

Clavicular periosteal reaction, presumably due to surgical trauma to the clavicular periosteum, was seen following 5 of the 35 procedures. In only 1 of these could a postoperative wound infection have played a prominent causative role. In all there was a definite calcific or osseous deposition of varying character in relation to the upper border of the clavicle. Only in Case I (Figure 2B), where an osseous spur was present, was this type of change obvious. In the 4 others it appeared as a linear calcific shadow lying parallel to and above the upper border of the clavicle. This is not to be confused with the normal soft-tissue shadow accompanying the shadow of the clavicle. It is distinguished by its greater density and by its lateral extension beyond the skin reflection.

An occasional adventitious effect is a diaphragmatic paralysis due to accidental injury to the phrenic nerve.

An interesting incidental feature is the

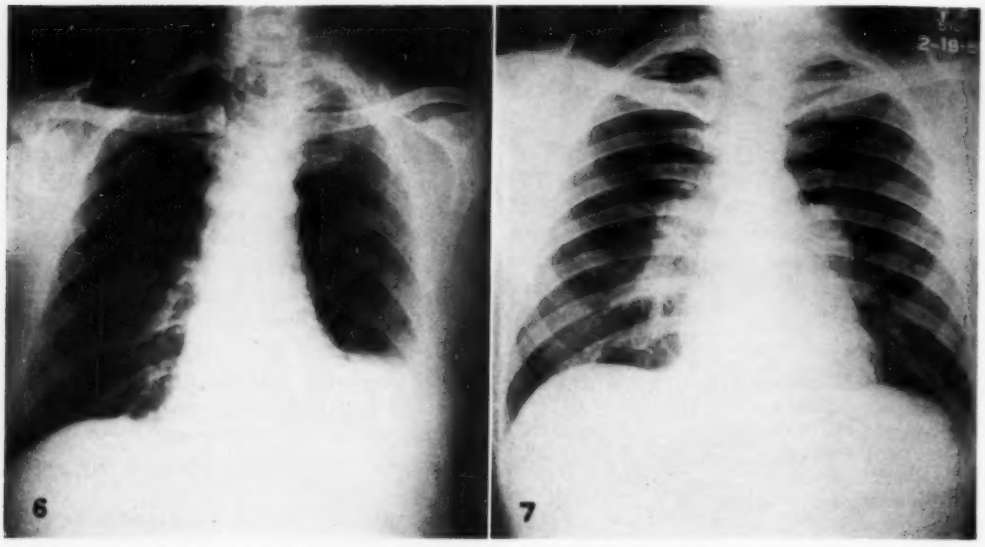

Fig. 6. Case V. The typical changes of radical neck dissection on the right side suggest that left pleural effusion is probably malignant in origin.

Fig. 7. Case VI. Typical changes of radical neck dissection on the right side suggest that enlarged hilar lymph nodes are probably of malignant origin. This case proved to be Hodgkin's disease.

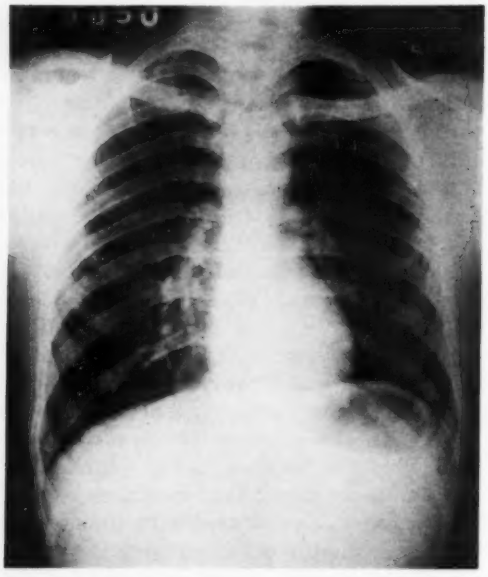

Fig. 8. Case VII. Postero-anterior roentgenogram of the chest in a 22-year-old asymptomatic white male. Changes resulting from a left radical neck dissection are shown, including periostitis of the clavicle. Multiple small nodular densities in both lungs were therefore attributed to metastatic cancer. Investigation of the history revealed a previous resection of the left submaxillary gland followed by radical neck dissection for metastatic adenocarcinoma, primary in the testis.

enhancement of these changes on the miniature photofluorograms, as illustrated in Case 4.

If less than two specific roentgenographic alterations were present, as was true in 6 of the 35 dissections, previous surgery was considered not recognizable. Of the 6 patients, 1 had a radical dissection plus contralateral infrahyoid dissection for carcinoma of the thyroid. In 1 of the bilateral cases the initial dissection resulted in typical roentgenographic changes but the second operation restored the symmetrical status and the abnormality was no longer discernible. In a third patient, there were chronic infiltrate and pleural thickening on the opposite side, so that the apex on the defective side appeared relatively clear even prior to surgery.

A suggestive correlation was observed between the size of the patient and failure to manifest these stigmata of surgery: all of the patients with negative findings were of obese or stocky build. This seemed to be valid for the modifications deriving from both the soft-tissue defect and the loss of shoulder support.

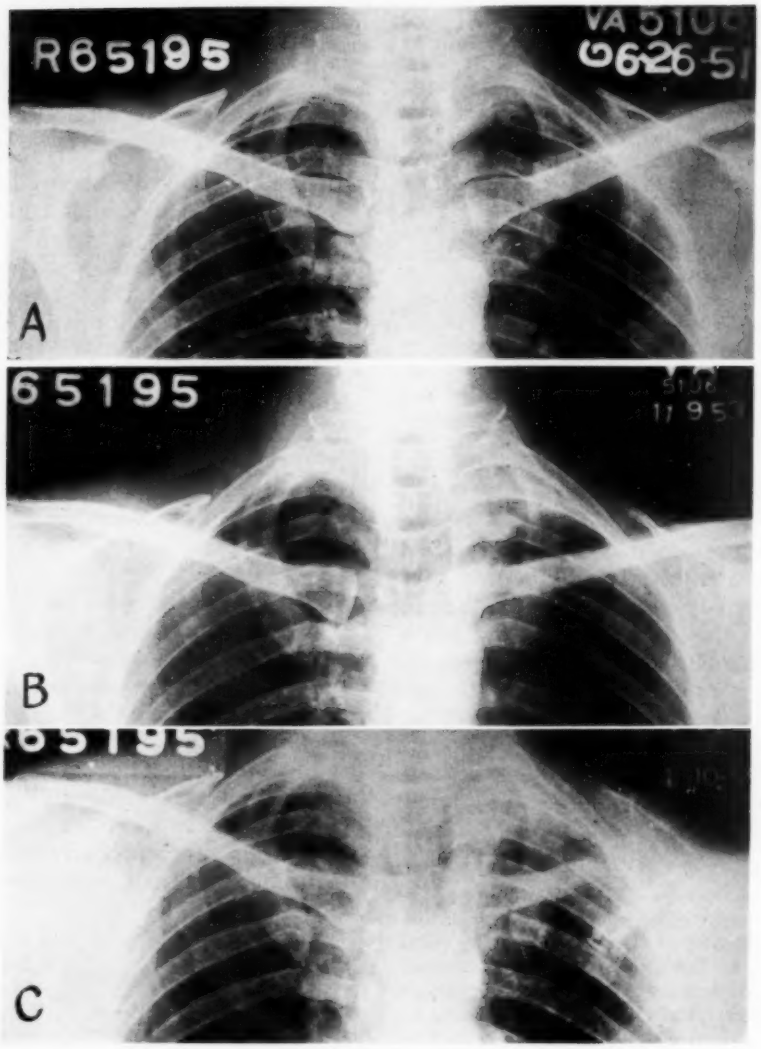

Fig. 9. Case VIII. A. Roentgenogram of both apices prior to radiation therapy. Inflammatory changes on both sides are shown, especially in the left apex, where there is also some emphysema. B. Study made twenty-eight months after radiation therapy, demonstrating marked diminution in the size of the left cervical soft tissues and some flattening of the apex of the left lung. A loss of the sternomastoid shadow, slight shoulder drop, thickening of the pleura, and pulmonary fibrosis are also shown. Changes in the trabeculae of the clavicle could be observed in the original film but are not well reproduced here. C. Roentgenogram four and a half years after radiation therapy, showing increased fibrosis and scarring of the left apex, with retraction of the trachea. There is now a pathological fracture of the clavicle. All the changes are no doubt due to the therapeutic irradiation. The difference in the appearance of the clavicle from that following surgical neck dissection is striking.

To illustrate the practical usefulness of identification of this condition, the following cases are presented:

CASE V: A 59-year-old white male had a right radical neck dissection on Oct. 18, 1950, for undifferentiated carcinoma of the thyroid. Radiation therapy for a recurrence in the neck was given in October 1954. The conspicuous alterations characteristic of neck dissection on the right (Fig. 6)

suggested the presence of cancer and the left pleural effusion was therefore considered to be probably of malignant origin.

CASE VI: A 23-year-old white male had a right Crile neck dissection and mediastinal exploration on June 25, 1951, for Hodgkin's disease. The hilar lymphadenopathy noted here (Fig. 7) is of a type often seen with sarcoidosis, but by recognition of the signs of radical neck dissection, one could from this single chest roentgenogram confidently suggest a malignant lymphadenopathy.

CASE VII: A 20-year-old white male had a left Crile neck dissection on Oct. 23, 1953, for adenocarcinoma of the left submaxillary gland. He became asymptomatic and returned to college. A follow-up roentgenogram (Fig. 8) dated June 27, 1955, showed a small nodular infiltrate in the lung fields, as well as several of the findings permitting recognition of a previous radical neck dissection on the left. Without any history it was thus possible to suggest the malignant nature of the nodular densities.

Other conditions may mimic the alterations we have described for radical neck dissection. Any process wherein there is paralysis of the sternomastoid and trapezius muscles, plus atrophy of the soft tissues of the shoulder, such as may be produced by a neurological lesion involving the spinal accessory nerve, will reproduce some of the commoner changes described. The following case presents a different type of situation, which provoked some perplexity:

CASE VIII: A white male at the age of 34 (July 1949) had a right orchiectomy for seminoma, followed by irradiation of the periaortic lymph nodes. Subsequently he had numerous recurrences, including lymph node metastases to both sides of the neck. All of these were treated by irradiation. Both sides of the neck were treated in July 1951, and the right side again in February 1952. There was no further recurrence when the patient was last seen in July 1955. The only surgery done in the left neck was a node biopsy.

In the roentgenograms (Fig. 9) the conspicuous features are the soft-tissue atrophy of the left side of the neck and shoulder and the pathologic fracture of the clavicle.

Before obtaining the history in this last case it was presumed that both the soft-tissue changes and the fracture could be due to a surgical procedure. We had not previously seen such a soft-tissue response to radiation, although radiation necrosis of the clavicle was considered. It is apparent that an old inflammatory process existed in the left apex before the present disease had been treated. Thus it seems that, rarely, radiation alone may produce some of the modifications usually attendant upon radical neck dissection.

SUMMARY

Radical neck dissection produces a number of definite changes of such character that it may be recognized in the majority of instances on the routine postero-anterior chest roentgenogram.

Details of the surgical procedure and the consequent roentgen changes are enumerated and explained.

The practical aspects of the identification of this procedure are discussed and simulating conditions mentioned.

VA Hospital
Minneapolis 17, Minn.

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SUMARIO

Alteraciones Roentgenológicas Consecutivas a la Disección Radical del Cuello

En un repaso de 33 casos en que se había ejecutado la una disección radical del cuello (en 31 unilateral; 2, bilateral), se descubrieron radiográficamente varias alteraciones bien definidas. En orden de su frecuencia, fueron: (1) pérdida de la sombra esternomastoidea, (2) hiperradiabiiidad del vértice, (3) defecto regional del tejido blando, (4) hombro caído, (5) periostitis clavicular, (6) parálisis diafragmática. La

presencia de dos o más de estas características se considera suficiente base para presuponer la ejecución anterior de una disección cervical.

El valor práctico del reconocimiento de estas alteraciones es triple: (*a*) puede facilitar al radiólogo, y hasta al clínico información que no obtendría de otra manera; (*b*) encaminará la atención del radiólogo hacia la histopatología que puede lógicamente esperarse como complicación de la cirugía o del proceso morboso subyacente; (c) puede ayudar al radiólogo a evitar el peligro latente de interpretar las alteraciones derivadas de la cirugía como proceso patológico espontáneo o anomalía anatómica.

Ciertos estados, que comprenden parálisis de los músculos esternomastoideo y trapecio, además de atrofia de los tejidos blandos del hombro, pueden producir alteraciones semejantes, y parece posible que, en raras ocasiones, esas alteraciones sigan a la irradiación.

Congenital Biliary Atresia with Emphasis on the Skeletal Abnormalities[1]

EMANUEL J. LEVIN, M.D.

CONGENITAL biliary atresia is a developmental defect resulting in the complete exclusion of bile from the intestinal tract. The severe hepatic damage consequent upon the biliary obstruction produces polyclinical abnormalities which have been reported in numerous publications (29, 33, 34). As far as can be determined, however, there has been no clear distinction made between the two varieties of osseous dystrophy found in this condition. The following two cases are presented to illustrate these differences, as well as many of the other abnormalities found in biliary atresia.

REPORT OF CASES

CASE I: D. P., a colored female, was born on July 29, 1952, and was first admitted to the Cincinnati General Hospital on Sept. 23, 1952, because of jaundice which had not been present at birth. The mother stated that the baby passed on the average four yellow stools daily and the urine was never dark.

Physical examination was normal except for scleral icterus. The stools were clay-colored and the urine dark. Serum bilirubin was 9.0 mg./100 c.c.

Since there was a discrepancy between the mother's observations concerning the color of the urine and feces and that of the examining physician, the possibility of one of the "inspissated bile syndromes" was considered. Despite the institution of a hydrocholeretic regimen to increase the flow of bile, the signs of obstructive jaundice persisted.

Laparotomy on Oct. 28 demonstrated a large cirrhotic liver and complete absence of the extrahepatic ducts and gallbladder. Since definitive surgery was impossible, a liver biopsy was obtained to ascertain the condition of the intrahepatic ducts and the abdomen was then closed.

On histologic examination the liver showed stasis of bile pigment with bile cast formation in the small biliary radicles. No large biliary ducts could be found. There were marked distortion of the hepatic architecture and perilobular fibrosis. In the surrounding stroma, numerous lymphocytes and a few neutrophils were seen. The microscopic diagnosis was "obstructive biliary stasis with acute and chronic cholangitis and early biliary cirrhosis."

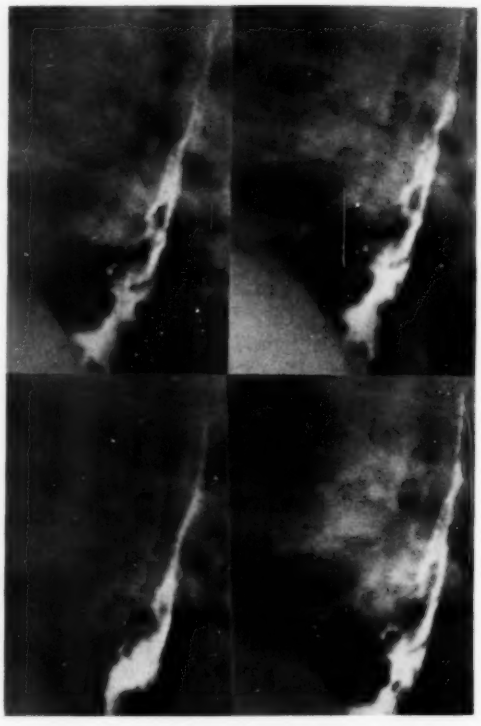


Fig. 1, Case I. Large esophageal varices (May 26, 1955).

The patient's history over the next three years was one of numerous respiratory infections interspersed with periods of comparative well-being. The serum calcium varied between 3.7 and 5.3 mEq/l (7.4 to 10.6 mg./100 c.c.), the serum phosphorus between 1.1 and 2.1 mEq/l (1.9–3.6 mg./100 c.c.), and the serum alkaline phosphatase between 14 and 26 Bodansky units. Moderately severe mental and physical retardation was noted, but the general state of nutrition was good. Hepatosplenomegaly was progressive, ascites became severe, and there were epistaxis and melena. Roentgen examination (Fig. 1) revealed large esophageal varices.

In April 1953, clinical evidence of rickets was detected and a skeletal roentgen survey was requested. Roentgenograms (Fig. 2) demonstrated generalized hypomineralization of bone with a coarse trabec-

[1] From the Department of Radiology, University of Cincinnati College of Medicine and the Cincinnati General Hospital. Accepted for publication in February 1956.

Fig. 2, Case I. Severe rachitic changes with genu valgum. Note the coarse demineralization, deep epiphyseal cartilage, cupping and fraying (April 8, 1953).
Fig. 3, Case I. There has been considerable improvement but evidence of rickets is still present (May 22, 1954).

ular pattern and severe rachitic deformities. The metaphyses were widened, cupped, and frayed, and the epiphyseal cartilages were increased in depth.

The vitamin D intake was increased progressively to 50,000 units of an aqueous solution daily and, in addition, a proprietary preparation of bile salts was given to improve fat absorption. Under this regimen there was a slow but progressive decrease in the severity of the rickets (Fig. 3). In May 1955, roentgenograms still showed rickets, delayed skeletal maturation, and a healing pathologic fracture. The degree of hypomineralization was best demonstrated in the skull, where the poorly calcified calvarium contrasted sharply with the normal radiopacity of the teeth (Fig. 4).

The patient was still alive in October 1955.

CASE II: P. C., a colored female, was admitted to the Cincinnati General Hospital on Sept. 9, 1953, because of jaundice present since birth (May 8, 1953). Physical examination showed scleral icterus, a small umbilical hernia, and hepatosplenomegaly. The stools were acholic and the urine dark. The total serum bilirubin concentration was 8.2 mg./100 c.c. A hydrocholeretic regimen was instituted to aid in the clearing of mucus or inspissated bile from the biliary tree, if by chance these were the cause of the obstruction, but the jaundice persisted.

Fig. 4, Case I. Lateral view of the skull showing severe undermineralization of the calvarium contrasting with normal radiopacity of the deciduous teeth.

Laparotomy on Sept. 28 revealed a large hobnailed cirrhotic liver. In a deep fissure between the right and caudate lobes, a cord-like fibrosed gallbladder was found. Further dissection exposed a short segment of the common duct, as well as a narrowed segment of a hepatic duct. Aspiration of these

structures produced a few droplets of clear mucus. An aqueous radiopaque medium was injected into each of the ducts, but roentgenograms demonstrated a lack of continuity of the ductal system, so that visualization of the intrahepatic ducts was not obtained. Since it was impossible to establish biliary drainage, the abdomen was closed without further procedure.

The subsequent course was one of numerous respiratory infections, episodes of brisk hemorrhage from esophageal varices (Fig. 5), and the development of crops of petechial hemorrhages. There was generalized cardiac enlargement, which was attributed to the severe anemia. Gradually increasing abdominal fullness resulted from the hepatosplenomegaly and ascites (Fig. 6). The single determination of serum calcium concentration showed 5.1 mEq/l (10.2 mg./100 c.c.). No serum phosphorus concentration studies were done.

Since there was never any clinical evidence of rickets, the maximum daily dose of vitamin D prescribed was 2,000 units. The dose of vitamin A was 10,000 units. Physical and mental retardation were present, as was delay in epiphyseal appearance. The fingers became clubbed (Fig. 7), but periosteal new bone formation did not occur.

A roentgenographic examination of the skeleton showed severe hypomineralization (Fig. 8), with lines of "growth arrest" in most of the metaphyses. The bones were short and under-tubulated. Widening of the medullary cavity was prominent, as was the thin, sharp line marking the zone of provisional calcification. The epiphyseal cartilages were narrowed, but no other abnormality in the growth zones was present.

The patient died on Aug. 1, 1955. Autopsy was not obtained.

DISCUSSION

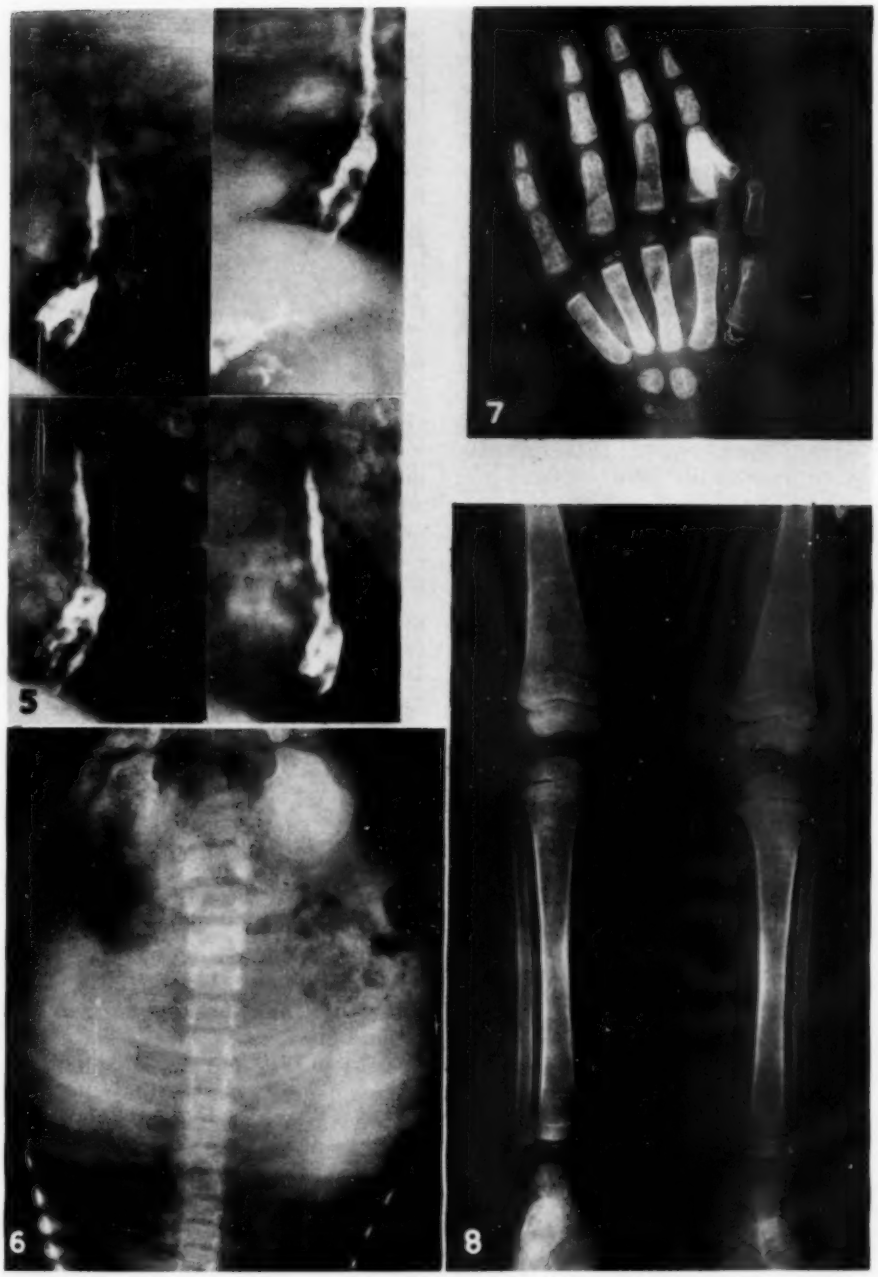
Embryology: There is no unanimity of opinion concerning the pathogenesis of biliary atresia, but the majority of investigators ascribe the process to a developmental abnormality rather than to an intrauterine hepatitis (27). Certainly the viral hepatitis of the neonatal period (15) has no pathologic resemblance to biliary atresia, and the haphazard distribution of atretic segments is more logically explained as the result of defects in embryogenesis.

The anlage of the liver (8, 10, 32) and its ducts develops as a hollow diverticulum, lined with entoderm, from the ventral aspect of the duodenum. Rapid enlargement of the diverticulum occurs simultaneously with an indentation in its anterior wall forming a caudal portion which differentiates into the common duct, cystic duct, and gallbladder, and a cephalic portion which becomes the liver and hepatic ducts. The cephalic portion proliferates rapidly, invades the septum transversum, and arborizes freely throughout the mesoderm into a sponge-like mass (42). This mass of hepatic cells engulfs the flanking vitelline and umbilical veins, which in turn subdivide and ramify between the developing cords of cells.

Most anatomists agree that the smaller distal biliary ducts develop from the more proximal larger ducts by continuous elongation and bifurcation (37). There is, however, no general agreement on the sequential phases of occlusion and patency of these ducts, but this is not germane to the overall result. In any event, during some phase of their development the ducts are obstructed by proliferated lining cells which by a process of vacuolation and coalescence of vacuoles, become completely patulous (12). Interruption of vacuolation is believed to result in atresia (51).

Pathogenesis: Congenital biliary atresia cannot be considered rare (29, 45). Large pediatric centers frequently have one or two cases in the active files, especially since the advent of more satisfactory methods of treating the severe respiratory infections which are prone to occur in these children. Although most patients die early in infancy, a significant number have survived for more than three and even as long as nine and twelve years (16, 33). It is the prolonged survival time associated with gradually increasing hepatic decompensation which permits the development of so many different manifestations of the anomaly, most of which are identical with the findings in chronic liver disease of adults (38). The tissue response to the hepatic disease varies in the adult and child only where there is a difference in the receptor organ, *e.g.*, rickets develops in infants but only osteomalacia is seen in the adult.

Common to all cases of congenital biliary atresia, even in the neonatal stage, are obstructive jaundice, cirrhosis (43), and hep-



Figs. 5–8, Case II

Fig. 5. Large esophageal varices at twenty months. Melena has been present for seven months.
Fig. 6. Hepatosplenomegaly and ascites.
Fig. 7. The small bones of the hand and wrist are hypomineralized, but there are no rachitic changes. Clubbing of the fingers is present.
Fig. 8. There is hypomineralization of all the bones visualized. The limbs are straight, the cortices thin, and the medullary cavity wide. Undertubulation of the shafts is seen, as are lines of "growth arrest."

atitis (49). The jaundice may not be clinically evident at birth and may escape detection for the first week of life if the significance of the clay-colored stools and dark urine is not properly evaluated. The absence or imperceptibility of jaundice, as in Case I, has been noted previously (33, 49) and is accompanied by relatively low bilirubin levels at birth. Prior to birth the bilirubin is dialyzed across the placental membranes into the maternal circulation.

If the infant survives for three to six months, both physical and mental retardation become obvious, but the general nutrition is surprisingly good and remains so throughout most of life (49). Many other abnormalities develop, some frequent, others rare. The following list is a partial recapitulation of the reported manifestations but excludes most of the abstruse chemical aberrations:

(*a*) Ascites and bleeding esophageal varices (3, 9).
(*b*) Splenic anemia (28). In 1 case there was reversion to a normal hemogram following splenectomy.
(*c*) A dimorphic anemia with a very cellular marrow, probably secondary to deficient storage of an antianemic principle (46).
(*d*) Hypoprothrombinemia with persistent bleeding. The prothrombin level will return to normal with the administration of vitamin K oxide.
(*e*) Decrease in the serum albumin concentration associated with elevation of serum globulin, particularly of the gamma globulin fraction. No change in the fibrogen concentration has been noted.
(*f*) Skin xanthomata (1, 36). These are associated with severe and prolonged hyperlipemia. In several cases the xanthomata decreased in number and size, paralleling a decrease in the degree of lipemia. Unfortunately this probably portends the terminal phase of hepatic disease.
(*g*) Vitamin A deficiency (4, 7, 33, 41) Although keratomalacia and xerosis have not been reported, epithelial atrophy and keratinizing metaplasia of the respiratory mucosa have been demonstrated at autopsy.
(*h*) Renal tubular disease (3, 9). This is an indistinct entity, but degenerative changes in the renal tubules and glomerulus have been frequently described.
(*i*) Clubbing of the fingers.

Skeletal Abnormalities: Radiographically there are two distinct types of osseous abnormalities. In both, the bones are deficient in mineral content and are unusually fragile, fracturing with minimal trauma but healing uneventfully. The epiphyseal centers appear late and there is severe dwarfism. There is also a delay in dentition and those deciduous teeth which do appear soon become green and carious (1, 20). Finally, both types of osseous dystrophy are found in icteric and nonicteric chronic hepatic disease (48).

That one type of skeletal abnormality is rickets (17, 18) has been established clinically, radiologically, and pathologically (Fig. 9), despite some dissenting opinions (11, 30). Roentgen examination demonstrates poorly mineralized bowed bones with a coarse trabecular pattern. The depth of the epiphyseal cartilage is increased, and the ends of the diaphyses are frayed, cupped, and widened. Coxa vara, genu valgum, triradiate pelvis, and other rachitic deformities are generally present. In this type, the serum calcium concentration is usually normal or slightly below normal and the serum phosphorus concentration is low. The serum alkaline phosphatase concentration is always elevated, but the high levels are due in part to the obstructive jaundice.

The second type of osseous dystrophy is unlike any vitamin, mineral, or nutritional disturbance known to the author. Roentgen examination in these cases demonstrates bones which are severely hypomineralized and have a homogeneous ground-glass appearance. The cortices are pencil-line thin and the medullary cavities are widened. Under-tubulation of the diaphyses is a prominent feature, so that the long bones have a box-like rectangular conformation. The depth of the epiphyseal cartilage is normal or decreased, and the adjacent zone of provisional calcification is smooth, thin, and of the same mineral density as the cortex of the shaft. There is no bowing of bone, nor are joint abnormalities seen. The subperiosteal hemorrhages of scurvy and the subperiosteal osteoclastic resorption of hyperparathyroidism are not present.

It has been impossible to correlate the radiologic and pathologic appearance of the non-rachitic osseous dystrophy, since only a few reports could be found which supplied both adequate roentgenograms and even a modicum of a pathologic description. In one case a simple osteomalacia was found (33). In another, the microscopic diagnosis was diminished growth and development of cartilage with moderate hyperplasia of marrow elements. No lipid-laden histiocytes were found (36). In a third case, a histologic diagnosis of severe atrophy of bone with lipoid histiocytosis of bone marrow was made, and an analysis of a specimen of bone yielded an increased calcium phosphate to carbonate ratio, the reverse of the expected findings in rickets (23, 24).

Despite the lack of pathologic confirmation and the fact that rickets and osteomalacia in childhood are usually correlatives, it is still possible that in this second type of osseous dystrophy there is at least an element of osteomalacia.

Anatomically, vitamin D deficiency rickets is a diphasic abnormality representing both a dyschondroplasia of the proliferating epiphyseal cartilage and hypocalcification of diaphyseal osteoid. When the epiphyseal cartilage fails to proliferate, the dyschondroplastic element does not appear and there are no rachitic epiphyseal changes. Since all patients with this dystrophy have severe skeletal retardation, the absence of rachitic changes in the presence of diaphyseal osteomalacia would not necessarily be contradictory. Delay or absence of epiphyseal growth and maturation is not only a regular concomitant of severe lack of vitamin D but experimentally it is also one of the deleterious effects of vitamin A deficiency (7, 41, 50). The lack of the latter vitamin is at times a prominent feature of biliary atresia. Blackfan (7), McLean (41), and Wolbach (50) state that the absence of vitamin A results in the cessation of proliferative activities of the epiphyseal cartilages, producing a narrow band of atrophic cartilage which is bounded on the metaphyseal side by a thin osseous plate. Periosteal bone growth continues, but remodeling ceases. Although roentgenograms of non-rachitic hepatic osseous dystrophy are consistent with the description of vitamin A deficiency, further confirmation must be available before its etiologic role is accepted.

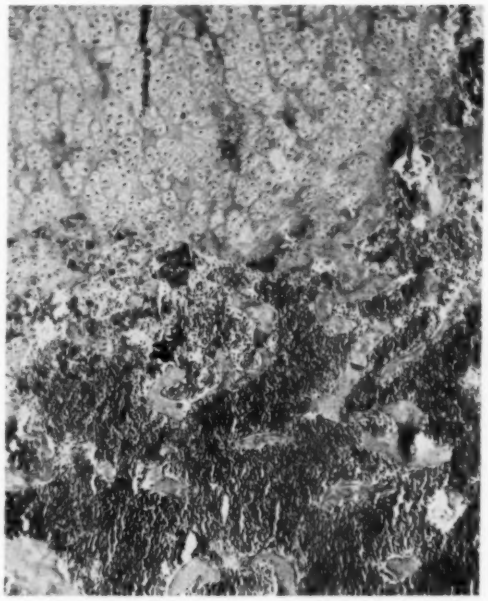


Fig. 9. Typical rachitic changes at the cartilage-shaft junction in a child with biliary atresia. Note irregular overgrowth of cartilage, producing characteristic broad epiphyseal plate. Courtesy of Dr. Ben Landing, Children's Hospital, Cincinnati, Ohio.

The underlying pathogenesis of the osseous abnormalities in biliary atresia is an enigma. Current opinion holds that the absence of bile from the intestine results in poor emulsification and poor absorption of fats, as well as the formation of calcium soaps. By this mechanism, vitamin D is not absorbed and calcium is lost in the feces.

This hypothesis is at best only a partial explanation, and there are many refutations (6). It has been demonstrated that many patients with biliary atresia will absorb half or more of the ingested fats and that a considerable increase in the fat content of the diet will not change the

percentage absorption (2, 38). Furthermore, the addition of bile salts should theoretically correct the fat and calcium loss and at the same time cure the rickets, but such is not the case. Lastly, the use of aqueous solutions of vitamin D orally or parenterally produces no significant response in the rachitic area until massive doses are used. Gerstenberger (18) and others (25, 26) feel that the liver in some way activates vitamin D and that in severe cirrhosis there is interference with this process.

The numerous reports of rickets and osteomalacia in non-icteric hepatic disorders lend substance to Gerstenberger's conclusions (48). These reports include cases of severe cirrhosis (5), diffuse malignant hepatoma (22, 28), hepatolenticular degeneration (12, 40), glycogen storage disease (39, 47) and galactosemia (15, 35). It may be that the common denominator is hepatocellular degeneration.

Diagnosis: One of the fundamental problems in the definitive diagnosis of jaundice is the differentiation of the obstructive from the non-obstructive form. Fortunately, the difficulties inherent in such an analysis in the adult are considerably diminished in the infant: the varieties of jaundice are significantly fewer and the advisability of temporization frequently permits sufficient time to elapse for spontaneous resolution of the abnormality.

The triad of unremitting progressive jaundice, acholic stools, and bilirubinuria in the neonatal period, persisting for at least four to six weeks, is presumptive evidence of congenital biliary atresia. The only other diseases demonstrating these signs, and of sufficient frequency to merit consideration, are viral hepatitis, erythroblastosis, and the "inspissated bile syndrome" (31). Each of these conditions may demonstrate all the ancillary signs of biliary atresia as well as its complications.

Viral hepatitis is being recognized with increasing frequency in pediatric practice and is usually manifested as a mild cholangitis with non-obstructive jaundice. The severe cases do not present any features distinguishing them from biliary atresia, and laboratory and clinical examinations afford no conclusive information. Needle biopsy of the liver is an accurate diagnostic measure and, although not entirely innocuous, is obviously much less formidable than laparotomy (13).

Erythroblastosis may also be an occult problem, but most cases can be differentiated from biliary atresia by the fluctuating jaundice and the presence of bile pigment in the stools at some time during the course of observation. In rare instances, overwhelming hemolysis is associated with severe hepatitis (40) and with obstruction of the biliary radicles by thick inspissated mucinous bile (14). Even in these cases the diagnosis is readily established by hematologic criteria: a positive Coombs' test, severe progressive anemia, and the demonstration of Rh incompatibility.

The "inspissated bile syndrome" is an abnormality of unknown etiology (21). It is probable that in many if not most instances this is a variation or a misdiagnosis of erythroblastosis or hepatitis (13). Pathologically, the cases are distinguished by occlusion of the biliary ducts by thick viscid, tenacious secretions which frequently undergo spontaneous dissolution so that a free flow of bile is re-established.

In the event that laparotomy is necessary, either as a diagnostic or therapeutic measure, it is essential that the extrahepatic ducts be visualized in their entirety, particularly if definitive procedures are attempted. The most reliable method of demonstrating the anatomic integrity of the extrahepatic ducts is operative cholangiography by any available route. The injection of the aqueous radiopaque medium should be made both proximally and distally with sufficient pressure to outline the larger intrahepatic ducts as well as any narrowed segments of the extrahepatic pathways. Roentgenograms in the anteroposterior and oblique projections will delineate these pathways and facilitate determination of the optimum surgical procedure.

Treatment: The only therapeutic proce-

dure of value in biliary atresia is surgical correction of the abnormality (21, 34). The operative technic is of necessity dependent upon the site and degree of the anomaly. Those patients with complete intra- or extrahepatic atresia are not amenable to surgical intervention, while the others may be cured by anastomosis of one of the hepatic ducts, the common duct, or the gallbladder, to the duodenum.

The preoperative management includes, in addition to the requisite delay of four to six weeks (21), restitution of blood hemoglobin and cell levels to normal values by transfusion and the administration of vitamin K parenterally to correct the low prothrombin levels. Operative intervention, however, should not be unduly postponed, since the severity of cirrhosis will increase.

The medical management of biliary atresia is purely supportive, but long-term survivals have been obtained. Almost all of these children become mentally and physically retarded, despite careful attention to their metabolic and endocrine requirements.

The treatment of the osseous lesions is unsatisfactory, and a consistent response is not obtainable, even in the same patient. It is probably best to resort to aqueous vitamins A and D parenterally in huge doses, as well as oral calcium supplements and one of the varieties of citrate solution (24). Fractures are frequent but heal satisfactorily under routine orthopedic management. Prolonged total immobilization is contraindicated. Finally, these patients should receive the customary pediatric immunization, and meticulous attention to infection is required.

SUMMARY

Congenital biliary atresia is a nonfamilial embryologic abnormality which may involve a small segment of a duct or the entire intra- and extrahepatic pathways. Patients suffering from this condition may live for a number of years, during which severe hepatic damage ensues. Consequent upon the liver disease, a long train of disturbances follow, not the least of which are severe skeletal abnormalities. Roentgenographically, two types of osseous disease are seen: the first is indistinguishable from deprivation rickets and the second may represent the effects of a combined vitamin A and vitamin D deficiency. Surgical reconstruction offers the only chance of cure, and this is possible in approximately 16 per cent of cases.

Cincinnati General Hospital
Cincinnati 29, Ohio

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SUMARIO

Atresia Biliar Congénita, Haciendo Hincapié en las Anomalías Esqueléticas

La atresia biliar congénita es una anomalía embriológica no familiar que puede afectar un pequeño segmento de un conducto o todas las vías intra- y extrahepáticas. Los enfermos que padecen de esta dolencia pueden vivir varios años, durante los cuales sobreviene grave lesión hepática. Como consecuencia de la hepatopatía, se presenta una larga serie de trastornos, de los cuales no son los menores las anomalías óseas graves. Radiográficamente, obsérvanse dos formas de enfermedad ósea: la primera es indistinguible del raquitismo por privación y la segunda puede representar los efectos de una deficiencia combinada de las vitaminas A y D. La reconstrucción quirúrgica ofrece las únicas probabilidades de curación.

The Role of Irradiation in the Treatment of Primary Malignant Lymphoma of the Stomach[1]

HARRY W. BURNETT, M.D. and EARLE A. HERBERT, M.D.[2]

THE PRESENT study has been directed principally toward an evaluation of the role of irradiation in the management of primary malignant lymphoma of the stomach. In lymphoma elsewhere in the body, irradiation is usually regarded as the primary method of treatment, since the disease is responsive to irradiation and is usually much too widespread for control by surgical resection. It is conceivable that the same principle would apply to lesions primary in the stomach.

Many cases of malignant lymphoma apparently have a unicentric origin. In the region of the head and neck, for instance, where a primary focus may be detected readily and treated promptly, the survival figures are far superior to those obtained in cases arising in an obscure and often asymptomatic region, where the process may become widespread before it is detected. This has been demonstrated by Catlin (1) in a series of 50 patients with disease apparently confined to the head and neck region, 52 per cent of whom survived for five years or longer.

Similarly, a lymphoma of the stomach may produce symptoms and be amenable to therapy before the disease has become generalized. Since the diagnosis is not usually established prior to exploratory operation, the usual treatment is a gastric resection, which may or may not be followed by irradiation.

Only a few studies are available on the results obtained by resection of the stomach, either as the only means of treatment or with postoperative irradiation. From the Lahey Clinic, Marshall and Meissner (2) reported 22 cases of lymphoma of the stomach, excluding Hodgkin's disease, treated by primary surgical resection. Seven patients lived five years or more, but 2 of these required supplementary irradiation because of recurrent tumor. Crile, Hazard, and Allen (3) of the Cleveland Clinic have reported 5 survivals among 10 patients with gastric lymphosarcoma followed over five years. One of these was treated by resection only, the others by a combination of resection and irradiation.

The possible results obtainable with irradiation alone are difficult to demonstrate, since the definite diagnosis is not usually made until the time of gastric resection. If the tumor proves to be too extensive to permit a satisfactory resection, it is usually too extensive to be ideal for cure by irradiation, and treatment becomes limited to palliation.

In order to evaluate the maximum effectiveness of irradiation without preliminary gastric resection, it would be necessary to analyze a consecutive series of all patients, including those with early disease, rather than a series limited to advanced unresectable lesions. To our knowledge, no such study has been published, though individual case reports reveal a number of survivals beyond five years in patients with unresectable lesions treated solely by irradiation (4–7).

Archer and Cooper (6), in an excellent review of 94 cases from the literature treated variously by resection and/or irradiation, have shown that small localized lesions can be cured by resection. In cases with more extensive disease, "it would seem that irradiation alone would offer the greatest hope to the greatest number of patients."

Although the present study does not provide a group treated by irradiation alone, it does include a number of patients

[1] From the Department of Radiology, New York Hospital-Cornell Medical Center, New York, N. Y. Accepted for publication in February 1956.

[2] Present address, Medical Arts Bldg., Wausau, Wisc.

TABLE I: PATIENTS TREATED BY RESECTION ONLY
(Tumor believed to be fully removed by operation)

Series Number	Age and Sex	Pathology	Duration of Follow-up*	Duration of Survival
1	51F	Reticulum-cell sarcoma	16 yr.	3 yr., 11 mo.
2	47M	Reticulum-cell sarcoma	14 yr.	14 yr.
3	62F	Lymphocytic lymphosarcoma	12 yr., 10 mo.	12 yr., 10 mo.
4	55F	Lymphocytic lymphosarcoma	14 yr.	11 mo.
5	34F	Reticulum-cell sarcoma	12 yr.	11 yr., 4 mo.
6	65F	Reticulum-cell sarcoma	11 yr.	3 mo.
7	66F	Reticulum-cell sarcoma	8 yr.	16 days

* Maximum possible survival period, from date of diagnosis to July 1955.

with extensive residual disease after gastric resection (Table III). By the use of irradiation postoperatively, long term survivals were obtained despite widespread involvement. It is probable that the results might have been equally good if treatment had been limited to irradiation, without resection. Conclusive evidence is not available to contradict this possibility.

MATERIAL

The material studied consisted in a consecutive series of patients having a positive microscopic diagnosis of primary malignant lymphoma of the stomach, without known extra-abdominal metastases, from the clinics of The New York Hospital-Cornell Medical Center between January 1939 and July 1953. No cases have been omitted, and a complete follow-up of each has been obtained.

Since the total series consists of only 27 patients, the detailed data have been tabulated for convenient reference.

Of the 27 patients, 11 were males (41 per cent) and 16 were females (59 per cent). The age range for the group was from twenty-two to seventy-nine years, with an average of 44.5 years. There were 15 cases (55.6 per cent) of lymphocytic lymphosarcoma; 10 (37 per cent) of reticulum-cell sarcoma; 2 (7.4 per cent) of Hodgkin's disease. The results obtained are presented in the accompanying tables: Table I, results with resection only; Table II, results with resection and irradiation; Table III, unresectable cases with distant abdominal metastases.

DISCUSSION

All patients were explored, at which time biopsy was done. Whenever possible, primary resection of the involved portion of the stomach was performed. Those patients showing evidence of residual disease were referred for supplementary treatment by irradiation. It should be emphasized that the irradiated group consisted only of patients with disease which had spread beyond the limits of resection (consult Table II for details), whereas, those not receiving irradiation had disease apparently confined to the resected specimen. Consequently, the two groups are not statistically comparable, in that the former is composed of patients with advanced disease, and the latter of patients with localized disease. In spite of this inequality of case material, the survival figures are higher for the more advanced group, namely, that receiving irradiation.

The per cent survival at one, five, and seven years of follow-up is shown in Figure 1. From these figures it becomes apparent that irradiation plays a very essential role in the prolongation of life in primary gastric lymphoma.

Regarding prognosis by pathologic clas-

TABLE II: PATIENTS TREATED BY RESECTION PLUS IRRADIATION

Series Number	Age and Sex	Gross Residual Tumor (after resection)	Microscopic Diagnosis	Tumor Dose (r)	Duration of Treatment (days)	Duration of Follow-up*	Duration of Survival
8	43F	Anterior abdominal wall	Lymphocytic lymphosarcoma	2704	41	14 yr.	1 yr., 10 mo.
9	58M	Liver, pancreas, duodenum, local nodes	Lymphocytic lymphosarcoma	3654	56	12 yr.	10 yr., 7 mo.
10	45F	Local nodes	Reticulum-cell sarcoma	3106	34	11 yr.	10 mo.
11	30M	Local nodes	Lymphocytic lymphosarcoma	2696	20	7 yr., 5 mo.	7 yr., 5 mo. (alive)
12	41F	Omentum, retroperitoneal and local nodes	Lymphocytic lymphosarcoma	1602	37	8 yr.	7 yr., 7 mo.
13	79M	Local nodes	Lymphocytic lymphosarcoma	4690	49	6 yr.	1 yr., 11 mo.
14	34M	Pancreas, gastrohepatic ligament, local nodes	Hodgkin's disease	4200	57	5 yr., 7 mo.	5 yr., 7 mo. (alive)
15	69F	Pancreas, transverse mesocolon, local nodes	Hodgkin's disease	4350	28	5 yr., 6 mo.	5 yr., 6 mo. (alive)
16	59F	Gastrocolic region, local nodes	Reticulum-cell sarcoma	3200	41	5 yr., 3 mo.	5 yr., 3 mo. (alive)
17	40M	Local nodes	Lymphocytic lymphosarcoma	2800	42	4 yr.	1 yr., 5 mo.
18	67F	Local nodes	Lymphocytic lymphosarcoma	3780	31	4 yr.	4 mo.
19	22M	Pancreas, portal region, liver, mesentery of small bowel	Lymphocytic lymphosarcoma	3000	48	4 yr.	4 mo.
20	68F	Local nodes	Reticulum-cell sarcoma	4350	35	3 yr., 4 mo.	3 yr., 4 mo. (live)
21	48M	Local nodes	Lymphocytic lymphosarcoma	3363	41	3 yr., 1 mo.	3 yr., 1 mo. (alive)
22	60F	Local nodes	Lymphocytic lymphosarcoma	3030	41	3 yr.	3 yr. (alive)
23	22F	Esophageal and local nodes	Reticulum-cell sarcoma	4000	38	2 yr., 9 mo.	2 yr., 9 mo. (alive)
24	77F	Local nodes	Lymphocytic lymphosarcoma	3000	24	1 yr., 8 mo.	1 yr., 8 mo. (alive)

* Maxium possible survival period, from date of diagnosis to July 1955.

TABLE III: UNRESECTABLE CASES
(With distant abdominal metastases)

Series Number	Age and Sex	Pathology	Duration of Follow-up*	Duration of Survival	Comments
25	52M	Lymphocytic lymphosarcoma	12 yr.	4 mo.	Given palliative irradiation
26	45M	Lymphocytic lymphosarcoma	9 yr.	5 mo.	Given palliative irradiation
27	65M	Reticulum-cell sarcoma	8 yr.	2 mo.	Jejunostomy; no irradiation

* Maximum possible survival period, from date of diagnosis to July 1955.

sification, the number of patients is statistically limited; however, the findings suggest a more favorable prognosis for Hodgkin's disease than for reticulum-cell sarcoma, with lymphocytic lymphosarcoma intermediate. In each instance, the addition of irradiation improved the prognosis over that with resection alone. In view of the complex interrelationship of these three classifications, it is perhaps best to regard the entire group under the collective diagnosis of "malignant lymphoma." As an example, one of the patients originally showing the microscopic picture of Hodgkin's disease of the stomach had a neck node removed five and one-half years later showing the characteristics of reticulum-cell sarcoma.

RADIATION THERAPY TECHNIC

All patients were treated in essentially the same manner with 200- to 250-kvp x-rays with a half-value layer of 1.5 to 2.0 mm. of copper, at 50 or 70 cm. target-skin distance. Usually two anterior and two posterior portals of appropriate dimensions were cross-fired at the level of the affected region.

Figure 2 shows the calculated tumor dose and duration of treatment for patients undergoing resection and postoperative irradiation. In addition, the pathologic diagnoses and survival data are indicated. Since the three-year and five-year data are similar, three-year data have been plotted in order to provide a larger group for evaluation.

The random distribution of survivals, as well as pathologic diagnoses, within the time-dose coordinates suggests that a suitable dosage would be 3,000 to 3,500 r in about forty days. Individual tumor sensitivity to irradiation and extent of disease evidently were the deciding factors in many of the patients. One patient, for example, with extensive retroperitoneal nodes lived seven years and seven months following a tumor dose of only 1,600 r in thirty-seven days. On the other hand, another patient with disease in the regional mesenteric nodes lived just short of two years with a dosage of 4,690 r in forty-nine days.

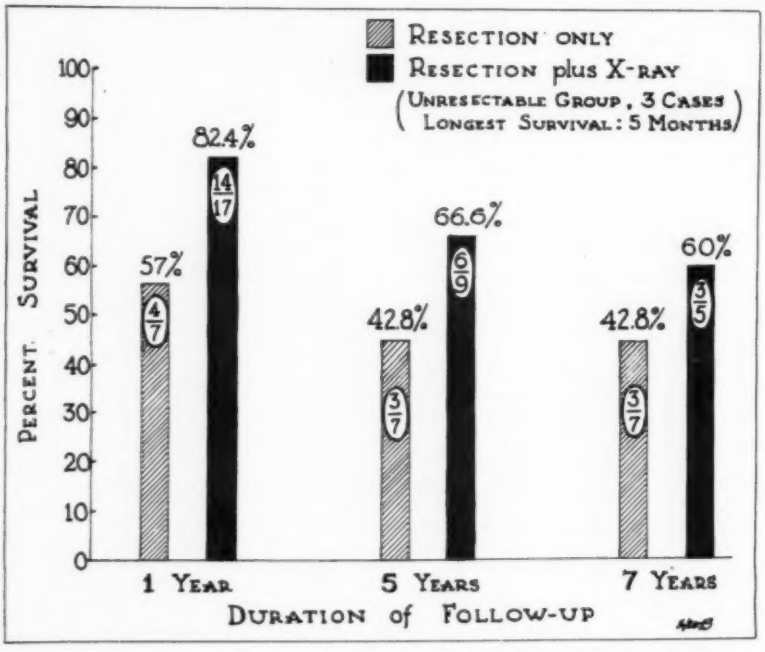

Fig. 1. Survival rates following resection alone and resection plus irradiation.

SUMMARY

1. Twenty-seven cases of primary malignant lymphoma of the stomach have been reviewed as to treatment and end-results. Particular attention has been given to the role and technic of irradiation therapy.

2. A review of the literature as well as the findings in the present study indicate that a five-year survival percentage above 60 per cent is obtainable in patients with primary malignant lymphoma of the stomach.

3. In patients treated by resection only, long-term survivals can be obtained if the disease is limited to the resected

specimen. In the present series 3 of 7 patients lived beyond ten years; the five-year survival for the group was 42.8 per cent.

4. With resectable lesions and involvement beyond the limits of resection the prognosis is favorable if an adequate course of irradiation is given. In the present series 66.6 per cent of such patients were alive five years after treatment.

5. Extent of disease was apparently the most significant factor in prognosis. Very localized lesions were curable by resection only. When involvement was beyond the margins of resection, long-term survivals were obtained by supplementary irradiation, providing the involvement could be encompassed by conventional technics.

6. Pathologic cell type had little differential influence in affecting prognosis, inasmuch as similar results were obtained with lymphocytic lymphosarcoma, reticulum-cell sarcoma, and Hodgkin's disease. The 2 patients with Hodgkin's disease are both still alive five years and six months, and five years and seven months. However, this could not be regarded as representative of a larger series.

7. A tumor dose of 3,000 to 3,500 r in about forty days appears to be appropriate in most instances. Remote metastases and individual cellular sensitivity factors seem to be more limiting factors.

8. Data are not available in the literature nor in this series to demonstrate the maximum possibilities of irradiation as the sole method of treatment. It is probable that equally good results should be expected if, following biopsy, patients were treated by irradiation alone, without preliminary resection, since long-term survivals are obtainable in patients with disease beyond the scope of resection.

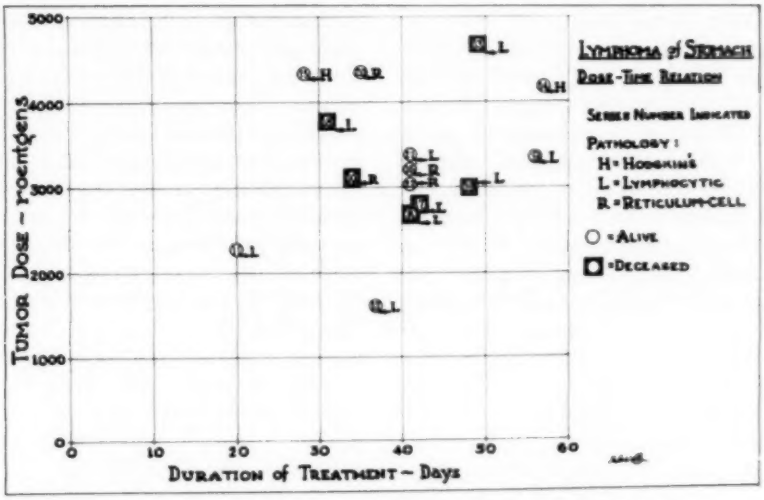

Fig. 2. Calculated tumor dose and duration of treatment in irradiated cases.

New York Hospital
525 East 68th St.
New York 21, N. Y.

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SUMARIO

El Papel de la Irradiación en el Tratamiento del Linfoma Maligno Primario del Estómago

Este estudio versa sobre una serie consecutiva de 27 enfermos en quienes se hizo un diagnóstico microscópico positivo de linfoma maligno primario del estómago sin metástasis extraabdominales conocidas, observados entre 1939 y 1953.

La extensión de la enfermedad resultó ser el factor más importante en el pronóstico. Las lesiones absolutamente localizadas resultaron curables únicamente con la resección. Cuando la invasión se extendía más allá de los bordes de la resección, obtuviéronse sobrevivencias a largo plazo con la irradiación complementaria, con tal que la zona invadida pudiera ser abarcada con las técnicas convencionales. El tipo histopatológico de las células ejerció poco efecto diferencial sobre el pronóstico, visto que se lograron resultados similares en el linfosarcoma linfocitario, el sarcoma reticulocelular y la enfermedad de Hodgkin.

En la serie actual, las sobrevivencias de cinco años llegaron a 42.8 por ciento en 7 enfermos tratados con la cirugía sola y a 66.6 por ciento en 20 que recibieron irradiación complementaria. Opínase que cabría esperar resultados igualmente buenos con la irradiación (consecutiva a la biopsia) como método único de terapéutica, dado que se obtuvieron sobrevivencias a largo plazo en sujetos cuya enfermedad quedaba fuera del alcance de la resección.

Intermittent Arteriomesenteric Occlusion of the Duodenum[1]

LOWELL S. GOIN, M.D.,[2] and STEFAN P. WILK, M.D.[3]

SOME THIRTY-FIVE years ago, arteriomesenteric occlusion of the duodenum was in great vogue medically and was a popular subject in medical writing. It appeared under various names, such as superior mesenteric artery syndrome, intermittent arteriomesenteric occlusion of the duodenum, duodenal regurgitation, chronic duodenal ileus, and frequently under the general term duodenal stasis. Although the diagnosis is essentially a radiological problem, it occupies a very insignificant place in recent radiological literature and in the textbooks.

It is our belief that intermittent arteriomesenteric occlusion of the duodenum is somewhat more common than is generally appreciated and that the possibility of its existence is not given proper consideration by most clinicians and radiologists, since it appears to be rather rarely recognized. Inasmuch as the condition is so readily overlooked and patients suffering from it are so often abandoned as neurotics, we feel that a review of the subject is warranted.

Duodenal stasis may be divided into two major groups: (*a*) chronic obstruction due to organic disease, as congenital bands, adhesions, malrotation of the intestine, neoplasm, etc., and (*b*) intermittent obstruction, mechanical in nature, due to compression of the terminal duodenum by the mesentery and its contents. Our consideration will be confined entirely to occlusion caused by arteriomesenteric compression of the duodenum, a condition characterized by intermittent interference with the passage of the gastroduodenal contents through the third portion of the duodenum. The nature of this syndrome will be better comprehended if the anatomy of the transverse duodenum and its relationships are reviewed.

The third portion of the duodenum, as it crosses the spine, is fixed in a compartment bounded posteriorly by the spine and the aorta, and anteriorly by the root of the mesentery containing the superior mesenteric artery, vein, and nerve (Fig. 1). Being so contained, it is affected by any process which encroaches upon this space. Thus increased lordosis of the spine diminishes the space posteriorly, and a short mesentery, marked loss of weight, and a redundant relaxed abdominal wall increase the dragging effect of the mesenteric root and consequently narrow the space anteriorly (1–9). The intermittent character of the condition and the precipitation of the attacks by fatigue and by nervous strain indicate that neuromuscular derangement is also an important etiologic factor (10).

The condition occurs most commonly in asthenic patients of a lean, slender habitus and is much more common in females than in males (8, 11, 12, 13). The intermittent symptoms may date from childhood, but they more frequently develop in middle age (8, 14). Chronic illness, sudden loss of weight, periods of mental worry, conditions leading to relaxation of the abdominal wall (such as multiple pregnancies) are all precipitating factors. Even in quite pronounced cases the diagnosis can at best be only suspected clinically; it is essentially a radiologic problem. The symptoms, which vary with the degree of obstruction, may mimic closely a variety of upper gastrointestinal disorders, the more so since the condition may be concomitant with hemorrhagic pancreatitis, gallstones, or with peptic ulcers,

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[2] Chief Radiologist, Queen of Angels Hospital, Los Angeles, Calif. Clinical Professor of Radiology, University of California at Los Angeles.

[3] Assistant Professor of Radiology, University of California at Los Angeles; Visiting Radiologist, Harbor General Hospital, Torrance, Calif.

which are associated with duodenal stasis in a high percentage of cases (8, 13, 18, 19). Typically the patient complains of epigastric fullness or bloating one to four hours after meals, occasionally associated with mid-abdominal cramps. Vomiting occurs only in quite severe cases (13). Characteristically, the symptoms are of a recurrent, intermittent nature, and partial or complete relief is often obtained in the knee-chest or recumbent position.

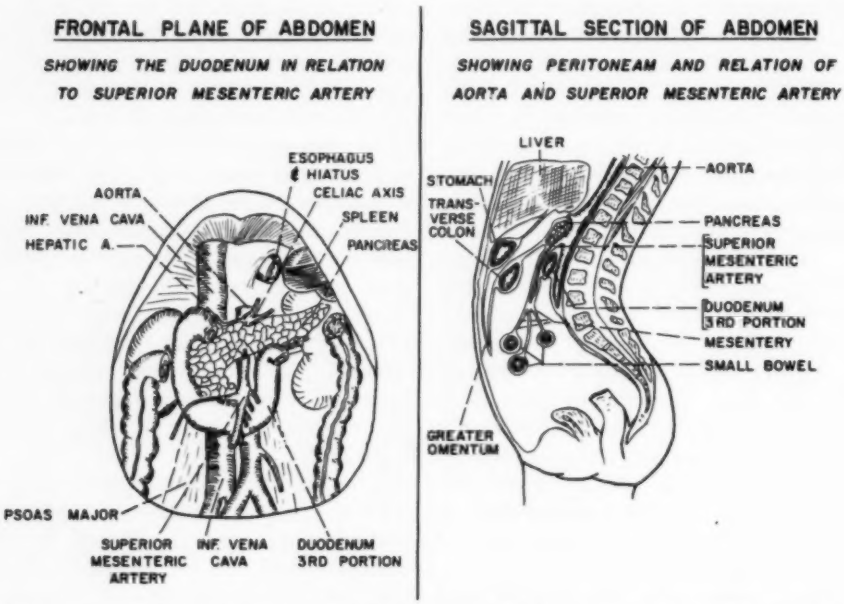

Fig. 1. Topographical relationship of the third portion of the duodenum in the frontal and medial sagittal planes. Modified from Gray's *Textbook of Human Anatomy*.

A positive diagnosis can be made only by careful fluoroscopic examination. With the patient erect, fluoroscopy usually discloses a rather long, vertical type of stomach, with dilatation of the proximal duodenum to the mid-line, where there is an abrupt obstruction of the third portion of the duodenum as it crosses the spine. The dilated portion exhibits strong, churning peristalsis, reverse peristalsis being quite prominent. If the patient is placed in the prone position, the duodenal retention usually disappears more or less completely—assumption of the knee-chest position or pressure over the lower abdomen has a similar effect (15)—but with return to the erect position the stasis recurs. Spot-films at the site of obstruction show a narrow, compressed lumen, but normal mucosa can usually be demonstrated. There is commonly a quite marked retention of gastric contents.

Attention should be called to certain diagnostic pitfalls. Churning peristalsis of the duodenum, for example, is not in itself a pathognomonic sign, since it is observed under various conditions (16). A moderate dilatation of the duodenum, with delay in passage through the transverse portion, is seen in many thin patients examined in the supine position, but it commonly disappears with resumption of the erect posture (17). Moreover, a variety of organic causes, such as tumors, congenital bands, malrotation of the intestine, adhesions, etc., may cause a similar occlusion. All these possibilities must be excluded. It must be remembered, also, that the absence of typical roentgen signs of arteriomesenteric occlusion of the duodenum during any given examination is by

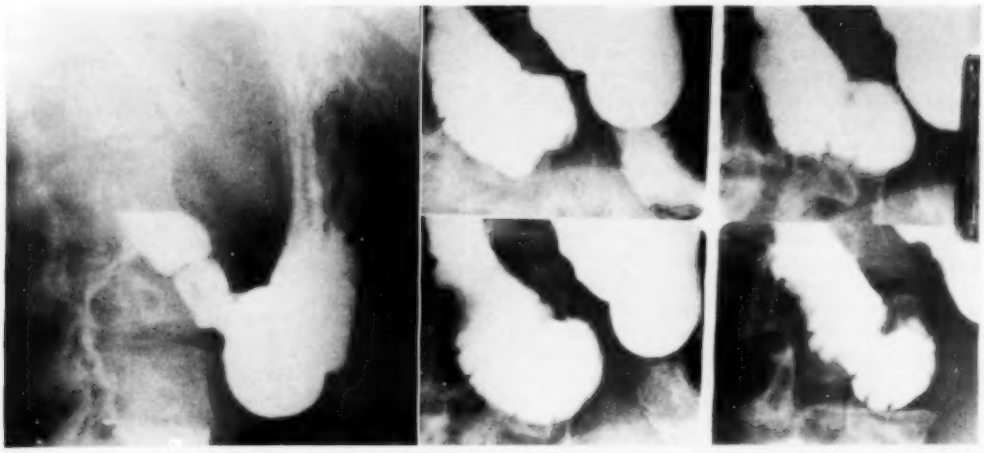

Fig. 2A. Case I. Left: Moderate dilatation of the transverse duodenum. Right: Spot films showing obstruction of the transverse duodenum and different phases of a strong peristaltic wave in the dilated proximal segment.

no means definitely conclusive and does not serve to eliminate the possible existence of this syndrome. As the condition is intermittent in nature, it follows that roentgen evidence of occlusion will be most manifest during an attack and will be absent or only moderately pronounced in the symptom-free period. Therefore, in all cases of clinically suspected intermittent duodenal occlusion, repeated gastrointestinal series are essential. These should be made, if practical, during an attack, since the condition is of a dynamic nature, strongly dependent upon the position of the patient. The diagnosis is made primarily on fluoroscopic evidence, the radiographs serving mainly as a permanent record and as an aid in evaluating coexistent disease.

The basic principles of therapy of this disorder are of prime importance. Wilkie (8), analyzing 75 cases of duodenal stasis, both organic and mechanical in nature, concluded that medical and postural treatment will relieve and cure a considerable number of patients with arteriomesenteric occlusion and that surgical correction should be reserved for those who fail to improve after an exhaustive trial of conservative measures. If surgery is considered, the operation of choice is duodenojejunostomy. Gastroenterostomy is definitely contraindicated and gives very poor results (20).

Fig. 2B. Case I. Roentgenogram obtained four weeks after duodenojejunostomy. Good functioning of the anastomosis (arrow). Relief of obstructive symptoms.

CASE REPORTS

CASE I: A 36-year-old female was seen in January 1954, with a history of twelve years of recurrent postprandial bloating, cramps, and dull pain radiating to the back, uninfluenced by medication. The symptoms first appeared after the patient's second pregnancy. She had consulted many physicians and had a great variety of treatment, including several laparotomies, with no relief. The symptoms became progressively worse, and finally she could tolerate only liquids and puréed foods.

Fluoroscopic study in the upright position revealed a marked dilatation of the proximal duodenum, with apparently complete obstruction in the transverse portion and with strong peristalsis in the dilated portion. In the prone position the obstruction was partially relieved (Fig. 2A). Arteriomesenteric occlusion of the duodenum was suggested and conservative management was tried without improvement.

In February 1954, a laparotomy was performed. At surgery spectacular active contractions and distention of the proximal duodenum as far as the level of the superior mesenteric artery were observed, but no organic cause for the obstruction was seen. A duodenojejunostomy was performed (Fig. 2B). The patient was completely relieved of her gastrointestinal symptoms and has remained well to the present time.

CASE II (Courtesy of Dr. Henry Lange): A 41-year-old female was hospitalized in November 1955, because of progressive malnutrition. She gave a history of recurrent postprandial cramps, occasionally associated with vomiting, persisting since early childhood. Lately she had vomited after nearly every meal.

An upper gastrointestinal series revealed a hugely dilated proximal duodenum with churning peristalsis (Fig. 3A), and arteriomesenteric occlusion was suggested. Various medical regimes, including diets, sedation, antispasmodics, and postural changes failed to bring about improvement. A duodenojejunostomy was performed (Fig. 3B) and at surgery no organic cause of duodenal obstruction was found, although the duodenum proximal to the mesenteric root appeared dilated. Since operation the patient has remained well.

CASE III: A 27-year-old male gave a history of duodenal ulcer of eight years duration, which was confirmed radiologically. Because of poor response to medical and dietary measures, a vagotomy and pyloroplasty were performed in March 1953. Following surgery, the patient did well for five months, at the end of which time attacks of postprandial epigastric cramps suddenly developed. These became progressively worse and finally were associated with vomiting after each meal. Relief was obtained only by assumption of the right decubitus position.

Radiologic study showed the proximal duodenum to be hugely dilated, with vigorous churning peristalsis (Fig. 4). There was almost complete obstruction of the transverse duodenum. In the right decubitus position the obstruction was relieved. Swallowing of ice-cold barium suspension had a similar effect for a few minutes—a phenomenon observed on two consecutive days. The patient could not retain any food.

A partial gastrectomy was performed. At operation the proximal duodenum down to the root of the mesentery appeared markedly edematous and somewhat dilated, but careful inspection failed to reveal any evidence of organic obstruction.

We believe that in this case the vagotomy is to be considered an etiological factor responsible for the arteriomesenteric occlusion of the duodenum.

CASE IV: A 72-year-old male was admitted to the hospital in September 1954, because of hematemesis. He gave a history of "bilious attacks" since early youth. Sometimes after a large meal, the epigastric cramps seemed to be associated with a "lump" in the mid-abdomen. The "lump" and discomfort disappeared when the patient doubled up in a chair or when he induced vomiting. The symptoms occurred mainly during fatigue and nervous strain. Five years prior to the present admission the patient was thoroughly investigated in a university hospital because he had vomited blood during such an attack. On discharge he was told that his trouble was a "nervous stomach."

An upper gastrointestinal series on admission revealed marked dilatation of the stomach and the proximal duodenum, with obstruction of the transverse duodenum (Fig. 5), relieved in the right decubitus position. With postural measures, the abdominal symptoms subsided and the bleeding stopped. Re-examination after several days of bed rest disclosed no duodenal obstruction, and the spot films of the transverse duodenum showed an intact mucosa. No cause of hemorrhage could be identified. A hemorrhagic gastritis was believed to be a plausible explanation. On postural exercises the patient remained symptom-free, and a repeat gastrointestinal series three weeks later was entirely negative.

CASE V: A 36-year-old female entered the hospital in December 1953, in an emaciated condition. Six months prior to this admission, she had undergone hysterectomy and thereafter began to have dizzy spells, vomiting of undigested food, and abdominal cramps occurring about half an hour after each meal. The most extensive studies (including two upper gastrointestinal series in our department) by numerous physicians failed to reveal the cause of the epigastric troubles. The symptoms persisted

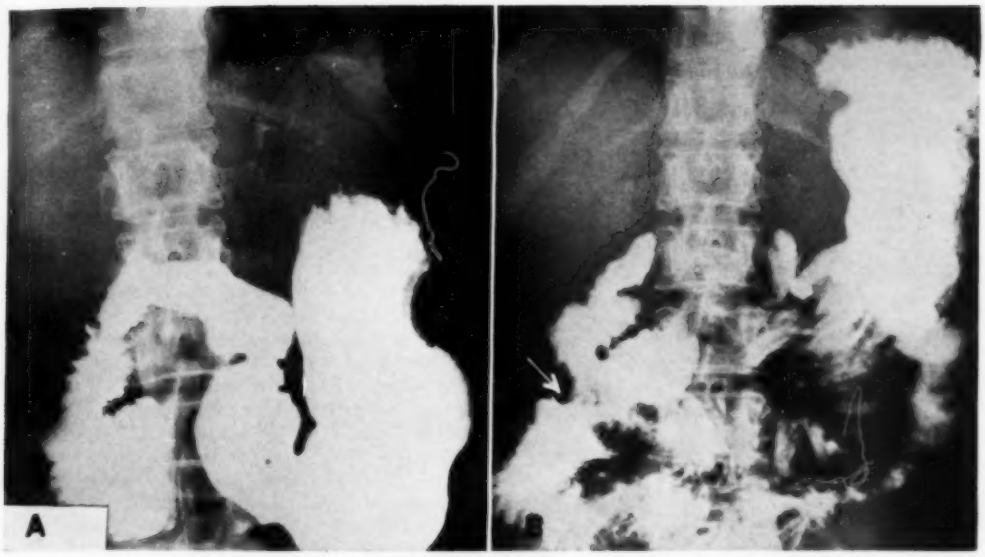

Fig. 3. Case II. A. Marked dilatation of the proximal duodenum, with complete obstruction at the level of the transverse portion.
B. Roentgenogram obtained several weeks after duodenojejunostomy. Good functioning of the anastomosis (arrow). Relief of obstructive symptoms.

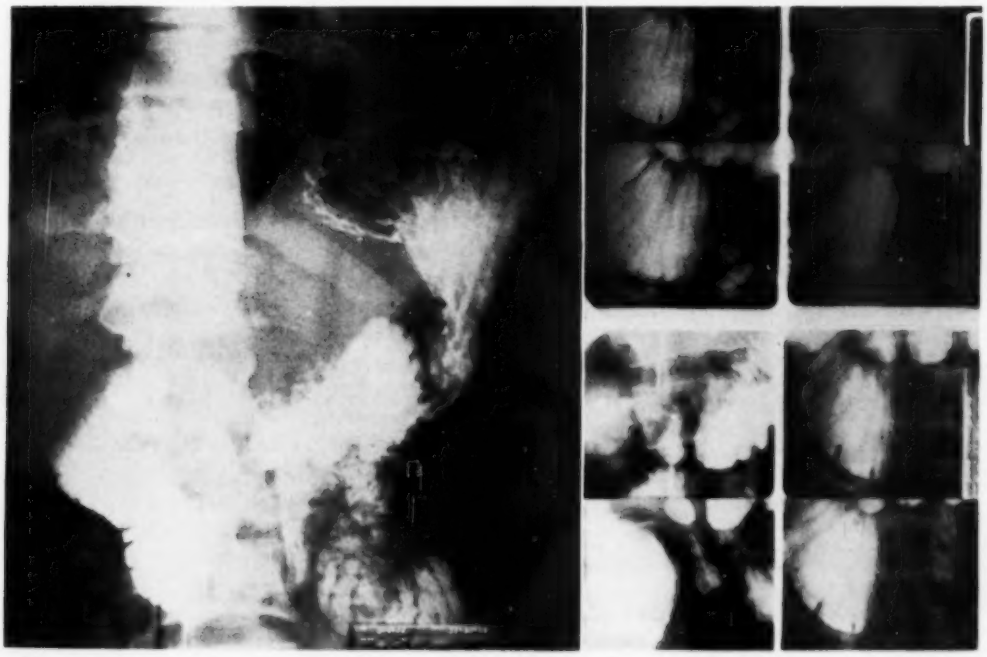

Fig. 4. Case III. Left: Large duodenal ulcer; marked dilatation of the proximal duodenum with obstruction at the level of the transverse portion. Right: Spot films showing the dilated duodenum and the obstruction site in detail.

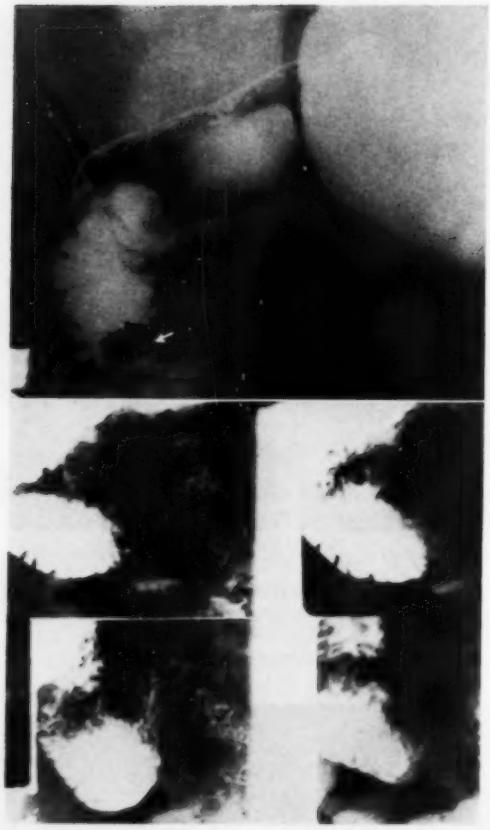

Fig. 5. Case IV. Above: Filling defect (arrow) on the superior anterior aspect of the transverse duodenum and marked dilatation of the stomach and the duodenum proximal to it. Below: Spot films of the filling defect area three days later, showing intact duodenal mucosa; no filling defect; no obstruction.

vomiting became more frequent, and the vomited undigested food was mixed with blood. Finally a third upper gastrointestinal series, made within a few months in our department during an attack of epigastric cramps, revealed an obstruction of the transverse duodenum, with dilatation of the proximal segment and violent peristaltic rushes in the dilated portion (Fig. 6A). The prone position relieved the obstruction to some extent and an arteriomesenteric compression of the duodenum was suggested.

Five days later, without any trial of postural or other conservative measures, a posterior gastroenterostomy was performed. At surgery the wall of the proximal duodenum appeared thickened, but no evidence of organic obstruction was identified. The patient experienced no relief and continued to have epigastric cramps with vomiting. Re-examination of the upper gastrointestinal tract showed poor functioning of the gastroenterostomy and obstruction at the transverse duodenum with dilatation of the proximal segment even more marked than it had been prior to surgery (Fig. 6B). Gastroscopic examination demonstrated the presence of hemorrhagic gastritis.

In this case, gastroenterostomy proved to be an extremely unsatisfactory procedure, which is in close agreement with the various cases reported in the literature.

CASE VI: A woman 25 years old presented herself for examination because she had suddenly noted rather large amounts of blood in the stool. She had no symptoms whatever and had never had abdominal pain, nausea, or vomiting.

An opaque enema study showed a quite extensive defect in the distal portion of the transverse colon (Fig. 7A). On exploration this lesion was found to be an adenocarcinoma, and the transverse colon was resected. When the anastomosis was made, the mesentery was shortened and immediately clinical signs of arteriomesenteric occlusion developed, namely, nausea, vomiting, and cramp-like pains in the upper abdomen.

Examination of the upper gastrointestinal tract showed almost complete obstruction of the duodenum near the duodenojejunal juncture (Fig. 7B), with violent peristaltic movements and rushes of reverse peristalsis.

DISCUSSION

In reviewing the literature, one frequently finds the statement that arteriomesenteric occlusion of the duodenum is a rare disorder, but no definite statistical data are available. It seems that its incidence has a somewhat endemic character. In institutions where the radiologists and clinicians are familiar with the condition, and where the radiologists look for it, there is found now and then a typical case requiring and responding to medical or possibly surgical therapy. For a radiologist conscious of the existence of this syndrome, it is relatively rare, but important enough to be sought in all unexplained abdominal disorders. When the radiologist is quite unfamiliar with the condition, it is for the most part overlooked or misinterpreted, and what is actually a rare disorder becomes for him non-existent.

In February 1953, we suggested this diagnosis after having examined the wife of a very competent surgeon and were sur-

Fig. 6. Case V. A. Marked dilatation of the third portion of the duodenum, with obstruction distal to it.
B. Roentgenogram obtained three weeks after gastroenterostomy. Poor functioning of anastomosis; dilatation of the proximal duodenum and obstruction of the transverse portion more marked than prior to gastroenterostomy.

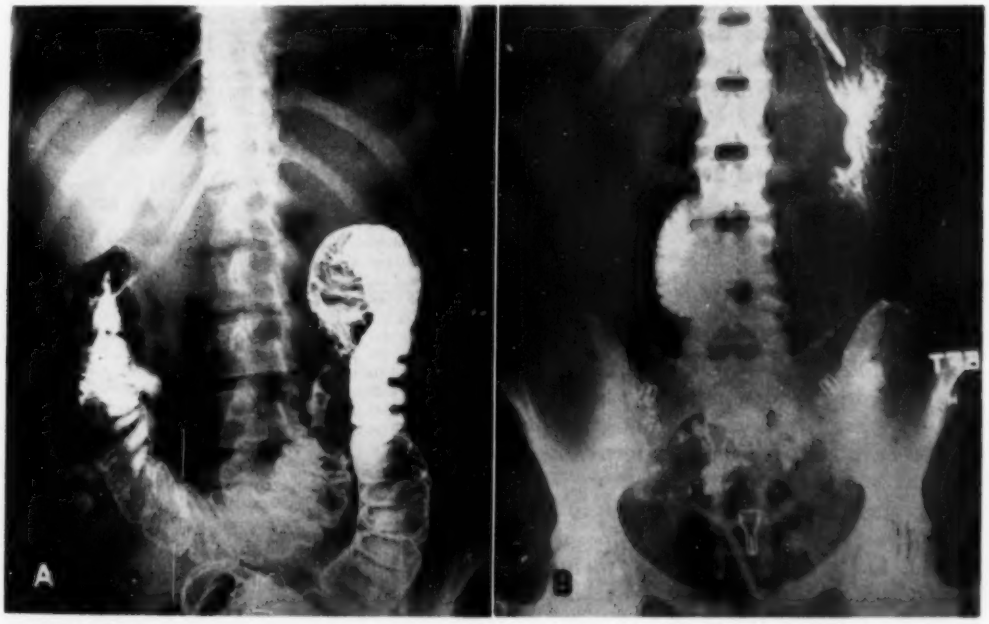

Fig. 7. Case VI. A. Opaque enema study showing defect in distal portion of transverse colon.
B. Roentgenogram obtained after operation, showing almost complete duodenal obstruction near the junction with the jejunum.

prised to learn that our hospital staff was quite unfamiliar with the disorder and that only one such case was to be found in the hospital records. This prompted us to start a careful search. In 1500 consecutive upper gastrointestinal series at the Queen of Angels Hospital (of which about 30 per cent showed radiologically some gross gastrointestinal lesion) we found 5 cases of arteriomesenteric occlusion of the duodenum. All were clinically symptomatic, required therapeutic measures, and showed typical roentgen signs.

A similar search was conducted, between June and December 1954, at Harbor General Hospital, Torrance, by the residents in radiology. In this period, 580 upper gastrointestinal series were done, of which 36 per cent showed some gross gastroduodenal disorder. Among these were 2 cases which clinically and radiologically were consistent with arteriomesenteric occlusion of the duodenum. In both hospitals the incidence was roughly 1 case per 300 consecutive upper gastrointestinal series. Certainly the disorder is rare compared with other pathological conditions of the upper gastrointestinal tract, but it does occur frequently enough, and is important enough, to be borne in mind and to be looked for carefully.

SUMMARY

Arteriomesenteric occlusion of the duodenum is a clinical entity characterized by intermittent obstructive symptoms. It occurs mostly in patients of the asthenic habitus and is to be differentiated from duodenal stasis which is organic in nature. It is a relatively rare disease but in surveys in two hospitals was found approximately once among every 300 patients in whom upper gastrointestinal series were performed. Hematemesis was present in 2 cases and was probably due to hemorrhagic gastritis. Vagotomy was believed to be the etiologic factor in 1 patient.

Most of these patients will respond satisfactorily to medical and postural measures, as did 4 of the present series. Duodenojejunostomy is the operation of choice and should be reserved for severe cases in which conservative measures are not successful. It was done in 2 of our cases with a good outcome. Gastroenterostomy gives very poor results.

658 South Westlake Ave.
Los Angeles 43, Calif.

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SUMARIO

Oclusión Arteriomesentérica Intermitente del Duodeno

La oclusión arteriomesentérica del duodeno es una entidad clínica caracterizada por síntomas intermitentes de obstrucción. Ocurre mayormente en sujetos del hábito asténico, habiendo que diferenciarla del éstasis duodenal, que es de naturaleza orgánica. Se considera como dolencia relativamente rara, pero en encuestas verificadas en dos hospitales se encontró aproximadamente una vez entre cada 300 enfermos en que se ejecutaron series de estudios radiográficos en la porción superior del aparato gastrointestinal. En 2 casos había hematemesis, debida probablemente a gastritis hemorrágica. En 1 enfermo, la vagotomía parecía ser el factor etiológico.

La mayoría de estos enfermos responderá satisfactoriamente a providencias médicas y posturales, según hicieron 4 de la serie actual. La duodenoyeyunostomía es la operación de elección y debe reservarse para los casos graves en que fracasan las medidas conservadoras. Se llevó a cabo en 2 de estos enfermos con desenlace bueno. La gastroenterostomía está contraindicada y ha dado malos resultados.

Visualization of the Basilar, Cerebellar, and Vertebral Arteries During Carotid Cerebral Angiography[1]

BERNARD S. EPSTEIN, M.D., and JOSEPH A. EPSTEIN, M.D.

THE BASILAR AND cerebellar arteries are seldom visualized during carotid angiography. Their recent demonstration in three such examinations prompted us to review our angiographic records and the literature in a search for other instances.

The principle of reflux filling is often employed for complete carotid cerebral angiography. Compression of the right common carotid artery above the point of insertion of the needle, together with occlusion of the brachial artery by means of a blood-pressure cuff, may reroute the contrast medium back along the common carotid into the innominate and subclavian arteries and thence into the vertebral artery. Serial films exposed about three seconds after injection will visualize the vertebral and basilar arteries often enough to make this procedure useful (1).

A similar mechanism is operative with thrombosis of the right internal carotid artery. Shapiro and Peyton (7) noted retrograde flow of contrast medium during right percutaneous carotid angiography, resulting in visualization of the vertebral artery. King (3) observed reflux vertebral artery opacification in a case of intracranial occlusion of the internal carotid artery at the origin of its anterior and middle cerebral branches. Retrograde opacification of the vertebral and basilar arteries in a case of occlusion of the right common carotid artery at its bifurcation has also been reported by Wise and Foster (8). They regarded such a reversal of flow, accompanied by non-visualization of the intracranial branches of the internal carotid artery, as indicative of occlusion of that vessel.

An application of retrograde filling of the vertebral artery was advocated by Schaerer (6). In his open indirect method of vertebral angiography, the right common carotid artery and brachial artery are occluded, while the contrast medium is injected into the exposed common carotid artery just before the point of temporary occlusion, so as to enter the vertebral artery by way of the innominate and subclavian arteries. Vertebral angiography was performed by Gould, Peyton and French (2) by retrograde injection into the right brachial artery after its surgical exposure. This method often resulted in visualization of the carotid system as well. However, its applicability is limited, since it is less successful in adults than in children.

The entry of contrast material into the basilar artery through the posterior communicating arteries during carotid angiography was mentioned briefly by Lima (4). Schaerer noted filling of the internal carotid artery and a small portion of the anterior cerebral artery in at least 2 instances, by passage through the posterior communicating arteries, during vertebral angiography. Retrograde filling, by way of a prominent posterior communicating artery, of the basilar, posterior cerebral, and superior cerebellar arteries during carotid angiography was observed in a case of hydranencephaly by Poser, Walsh, and Scheinberg (5). In their patient the anterior and middle cerebral vessels were rudimentary.

AUTHORS' MATERIAL

Within the past year we encountered 3 cases of filling of the basilar and cerebellar arteries during the course of percutaneous right carotid angiography. In the first instance the patient had a thrombosis of the right common carotid artery. In the others, the posterior, superior, and middle

[1] From the Department of Radiology and the Division of Neurological Surgery, Department of Surgery, The Long Island Jewish Hospital, New Hyde Park, N. Y. Accepted for publication in January 1956.

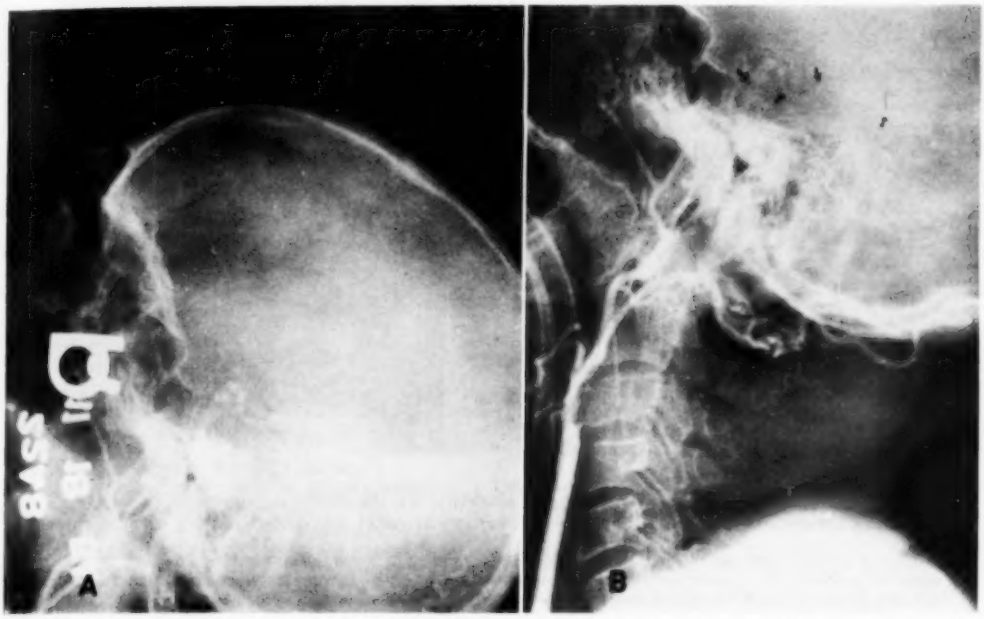

Fig. 1. Case I. A. Percutaneous right cerebral angiogram. The basilar, superior and middle cerebellar arteries are visualized. The internal carotid artery and its distribution are not opacified.

B. Right percutaneous cerebral angiogram repeated to show the needle point within the common carotid artery. There is an obstruction at the junction of the internal and external carotid artery, with most of the contrast medium passing along the external carotid circulation. Note that the basilar artery and the cerebellar arteries are again opacified (arrows). The large vessel leading toward the right orbit represents part of the collateral circulation which apparently has developed in this patient.

cerebellar arteries filled by way of the posterior communicating vessels.

CASE I: J. S., a 54-year-old male, complained of weakness of the left upper and lower extremities developing about three weeks before admission to the hospital. He had experienced a sense of pressure over the right eye for about two months. A gradual change in his personality had become evident to his family. He was increasingly forgetful, with varying periods of drowsiness and alertness. Along with the weakness of the left upper and lower limbs, there was awkwardness in the use of the left hand. The left side of the face also showed a gradually developing weakness. On the day of admission to the hospital the patient vomited frequently and had severe headache and complete left hemiplegia. His speech was incomprehensible and he was drowsy to the point of stupor.

Right percutaneous cerebral angiography revealed a block at the junction of the internal and external carotid arteries, with most of the contrast medium entering the external carotid circulation. The vertebral artery could be faintly identified in the neck. On two lateral studies the basilar artery was well visualized in its normal position and the superior and middle cerebellar arteries were opacified as well (Fig. 1).

At necropsy the diagnosis of thrombosis of the right internal carotid artery was verified. Inspection of the common carotid, subclavian, and innominate arteries disclosed only mild arteriosclerotic alterations. The basilar artery had filled because of reflux flow of Diodrast through the common carotid artery into the innominate and subclavian arteries and thence into the vertebral artery.

CASE II: B. W., a 74-year-old woman, was admitted to the hospital after falling down a flight of five steps. She had injured her head, lacerating the scalp. When admitted, she was conscious but complained of severe headache. There was a large area of ecchymosis in the right frontotemporal and periorbital regions, but physical examination disclosed no abnormalities.

Fourteen hours after the accident the patient was stuporous and her respirations were labored. No nuchal rigidity nor focal weakness appeared, but Babinski signs became positive bilaterally. Plain roentgenograms of the skull showed no fracture. The pineal body was not calcified.

Right percutaneous cerebral angiograms showed a pronounced shift of the anterior cerebral artery from left to right. On the right lateral view (Fig. 2A) the uppermost portion of the basilar artery was visualized, and the posterior, cerebral and superior cerebellar arteries could be identified. Apparently

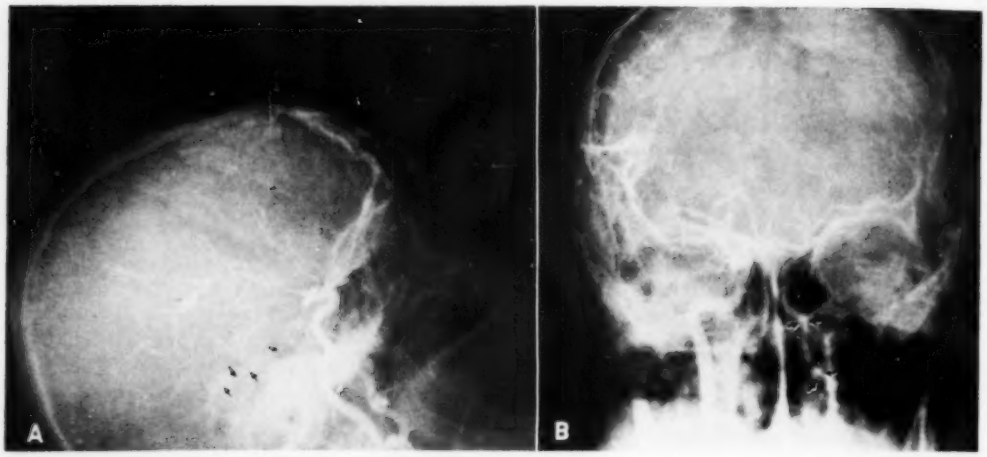

Fig. 2. Case II. A. Percutaneous right cerebral angiogram showing scanty filling of the right anterior cerebral artery. The middle cerebral vessel is poorly filled. Note that some of the Diodrast has traversed the posterior communicating artery to enter the superior cerebellar arteries (arrows). The basilar artery does not fill on this study.

B. Anteroposterior right percutaneous cerebral angiogram. The right internal carotid artery is well filled. The anterior cerebral artery contains very little contrast medium. Note the passage of the contrast medium through the posterior communicating artery with reflux of Diodrast down the basilar and left vertebral artery (arrows).

the contrast medium had entered the superior and middle cerebellar vessels through a prominent posterior communicating artery. The right anteroposterior angiograms (Fig. 2B) were of particular interest because the right internal cartotid artery, the basilar artery, and the left vertebral artery were opacified almost simultaneously. This confirmed the opinion that the course of the contrast medium had been through the posterior communicating artery, which permitted flow down the basilar and contralateral vertebral artery.

Left percutaneous cerebral angiograms showed a definite displacement of the middle cerebral vessels from the convexity of the skull, which was interpreted as indicative of a hematoma in the subdural or epidural space.

On all of the angiograms the degree of filling of the anterior and middle cerebral vessels through the internal carotid arteries was poor. It was postulated that increased intracranial vascular resistance permitted more than the average amount of medium to flow through the posterior communicating artery into the cerebellar, basilar, and vertebral arteries.

At operation, a large left cerebral extradural hematoma displacing the underlying brain inward for a distance of approximately 3 cm. was encountered. This extended from the frontal to the occipital poles. The bleeding appeared to be venous in origin, the middle meningeal artery remaining intact. A moderate-sized clot was also removed from the right subdural space.

The patient failed to respond to evacuation of the clots and died twenty-eight hours after admission to the hospital. Necropsy disclosed extensive damage to the right frontal lobe as well as to the major portion of the left cerebral hemisphere. Examination of the circle of Willis failed to reveal any abnormalities. The basilar artery likewise was normal. No evidence of thrombosis of the internal or external carotid arteries could be found.

CASE III: S. M., a 46-year-old woman, was admitted to the hospital because of protrusion of the right eye. This had developed insidiously but had increased in extent during the past three months. Plain roentgenograms of the skull disclosed a lytic meningioma involving the lateral two-thirds of the right lesser and greater wings of the sphenoid. Right lateral percutaneous cerebral angiography (Fig. 3) showed no displacement of the anterior or middle cerebral arteries. During the arterial phase, the posterior communicating artery was revealed as a relatively wide vessel with free flow of the contrast medium into the posterior cerebral, the basilar, and the superior cerebellar arteries. The basilar artery filled to the level of the inferior aspect of the clivus. The vertebral artery was not opacified.

At operation the diagnosis of a sphenoid-wing meningioma was confirmed.

COMMENT

Notations of visualization of the vertebral, basilar, and cerebellar arteries during carotid angiography are infrequent. This condition becomes self-evident roentgen-

ologically when contrast medium fills the common and external carotid arteries without entering the internal carotid artery. The site of obstruction often is at the bifurcation of the common carotid. The diagnosis under such circumstances is occlusion of the internal carotid artery by thrombosis. In these cases it is desirable that the injection site be included on the films. Otherwise, it might be assumed erroneously that the vertebral artery had been entered. However, in the usual course of percutaneous vertebral arterial angiography the opacification is quite dense, while with reflux filling the density of the vertebral artery may be relatively faint because of dilution.

Our last 2 cases indicate that occasionally the posterior communicating artery may be of sufficient caliber to permit flow of contrast medium into the superior cerebellar artery. The possibility that supratentorial intracranial disease which causes obstruction to the passage of contrast medium during the course of angiography may facilitate such visualization is suggested by our second case. This supposition is strengthened by the evidence presented by Schaerer and Poser, Walsh, and Scheinberg.

The question as to the incidence of opacification of the basilar, cerebellar, and vertebral arteries during the course of carotid angiography is interesting. We reviewed the last 100 percutaneous carotid angiograms obtained by us and were unable to find other such cases. Nevertheless, the fact that 3 instances appeared within a relatively short time compels us to consider that such visualizations may actually take place more often than we realize.

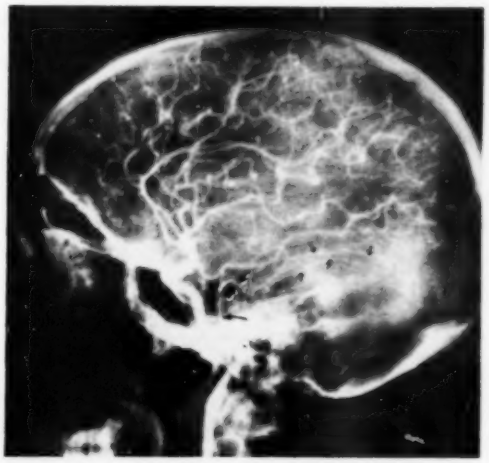

Fig. 3. Case III. Right lateral percutaneous cerebral angiogram. There is excellent filling of the anterior and middle cerebral arteries. In addition, the posterior communicating artery is filled, and the contrast medium flows into the basilar artery (arrow) and the cerebellar circulation (arrows).

SUMMARY

Three cases are reported in which the arterial structures in the posterior cranial fossa were visualized during the course of percutaneous carotid angiography. In 1 case this was incident to thrombosis of the internal carotid artery. In the remaining 2 cases, the contrast medium traversed the posterior communicating artery to enter the superior cerebellar and basilar arteries.

The Long Island Jewish Hospital
270–05 76th Ave.
New Hyde Park, N. Y.

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(Para el sumario en español, véase la página 745.)

Familial Fibrous Swelling of the Jaws

A New Case[1]

PATRICK RILEY, M.D., ORION STUTEVILLE, M.D., and ROBERT C. BROWN, M.D.

AN UNUSUAL multilocular "cyst-like" swelling of the jaws, apparently familial, was first described by Jones in 1933 (1). In 1938 he published a second account of his 3 patients, showing the progress of the condition in the intervening years (2). Seventeen years after the initial description, a further follow-up report appeared (Jones, Gerrie, and Pritchard, 3). In 1951, Caffey and Williams (4) described 5 cases of fibrous swelling of the jaws occurring in two families, and cited a case reported by Miller, for which, however, data were incomplete. We believe the following case to be the tenth recorded example of this unusual condition. It displays all the findings observed in the earlier cases, and the patient's father showed mandibular changes presumably due to a similar process in his youth.

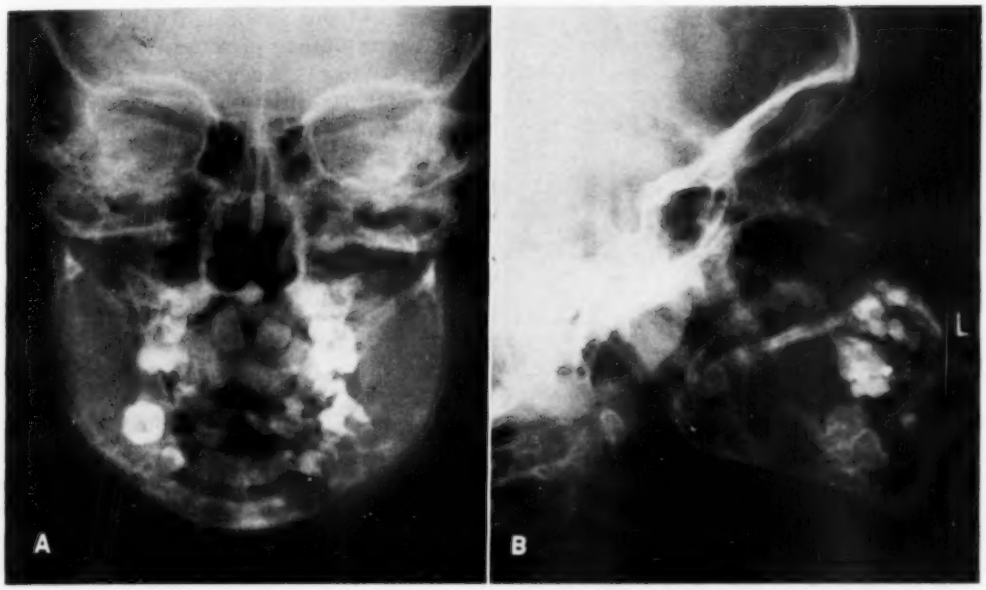
Fig. 1, A and B. Wide jaw and "squirrel-cheek" appearance, due to enlarged maxillae.
Fig. 2. Faulty position and alignment of teeth and widening of alveolar ridges.

CASE REPORT

A five-year-old boy was referred for roentgen examination of the jaws, which were moderately enlarged in a generalized fashion (Fig. 1). His appearance otherwise was normal. The maxillae were particularly prominent, stretching the skin of the cheeks and pulling the lower eyelids down, producing the "cherubic" aspect first noted by Jones. The alveolar ridges were widened and the teeth were irregularly spaced and poorly aligned (Fig. 2). There was no pain or tenderness, but enlarged nodes were felt in the submandibular and cervical regions. The mother stated that the child had had normal deciduous dentition until recent months. He had, in fact, been seen by a dentist only ten months before, and no abnormalities had been noted at that time. For the past few months, however, the deciduous teeth had been falling out rapidly, and the extremely irregular placement of those still remaining had become apparent. The swollen appearance of the jaws had not been noticed by the parents until it was brought to their attention.

Roentgen studies showed a multilocular cystic appearance of the entire mandible except for the condylar processes (Fig. 3). There was a diffuse increase in density of the maxillae and they were moderately enlarged, encroaching upon the maxillary sinuses. The teeth were poorly aligned and had rudimentary roots. Dental follicles for the

[1] From the Departments of Radiology and Oral Surgery, Chicago Wesley Memorial Hospital, and Northwestern University Medical School, Chicago, Ill. Accepted for publication in February 1953.



permanent teeth were irregularly placed and abnormal in size. The follicle for the second molar was absent, having been "crowded out" by the cystic areas.

A skeletal survey disclosed no other lesions. The blood chemistry was as follows: total protein 7.7 gm.; albumin 4.9 gm.; globulin 2.8 gm.; phosphorus 3.24 mEq/L; calcium 6.1 mEq/L; alkaline phosphatase 7.32 units; acid phosphatase 0.24 units. The hemogram and urinalysis were normal in all respects.

The child's father stated that he had had a localized swelling of the left side of his lower jaw in childhood. Radiographs of his mandible showed a completely inverted, unerupted molar tooth on the left side and an unusual appearance of the ramus of the right mandible, consisting of sclerosis and an abnormal trabecular pattern. The patient's uncle, his father's brother, also claimed to have had a swollen jaw in youth, for which many radium applications were given. The mandible was now deformed, both in contour and trabecular pattern, and these changes were believed to be at least partially due to a childhood occurrence of this same condition. The only sibling of the patient, a three-year-old girl, had normal jaws and teeth, clinically and radiographically. The mother gave no history of jaw enlargement, nor was there any in her family, and her dentition appeared normal. Radiographs of her jaw were not obtained.

Biopsy of the patient's jaw showed loosely arranged whorls of fibrous tissue with occasional giant cells (Fig. 5). The nuclei of the connective-tissue cells were uniform throughout. Decalcified sections of bone revealed trabeculae of normal thickness,

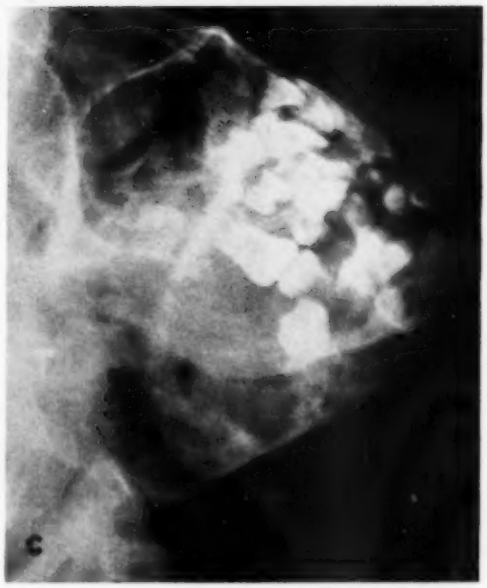


Fig. 3, A, B and C. Symmetrical mandibular involvement, showing large cyst-like spaces. The faulty positioning of the teeth is evident.

with connective tissue filling the spaces between. There was an occasional area of proliferating bone with somewhat more than the usual number of osteoblasts. A submandibular lymph node showed normal lymphoid follicles except for some increase in fibrous connective tissue and reticular fibers.

Fig. 4. Waters' projection, showing diffuse thickening of maxillae, with encroachment upon the maxillary antra.

the onset of this abnormality seems to parallel the beginning of resorption of deciduous tooth roots, suggesting "overaction" of normal resorptive processes with resultant pseudocysts which fill with fibrous tissue. The apparent decrease in the progress of the condition which has been observed during adolescence corresponds well in time with the natural decrease in tooth root resorption and the end of the deciduous tooth period.

SUMMARY

What is believed to be the tenth recorded case of familial fibrous swelling of the jaws, originally described by Jones, is presented. The patient was a boy of five years, whose father and uncle both gave a history and findings suggesting a similar process in their youth.

Although the microscopic examination of biopsy tissue from the mandible showed findings typical of fibrous dysplasia, the apparent familial occurrence and diffuse nature of the process in both the maxillae and mandible indicate that this case is another example of "familial fibrous swelling of the jaws."

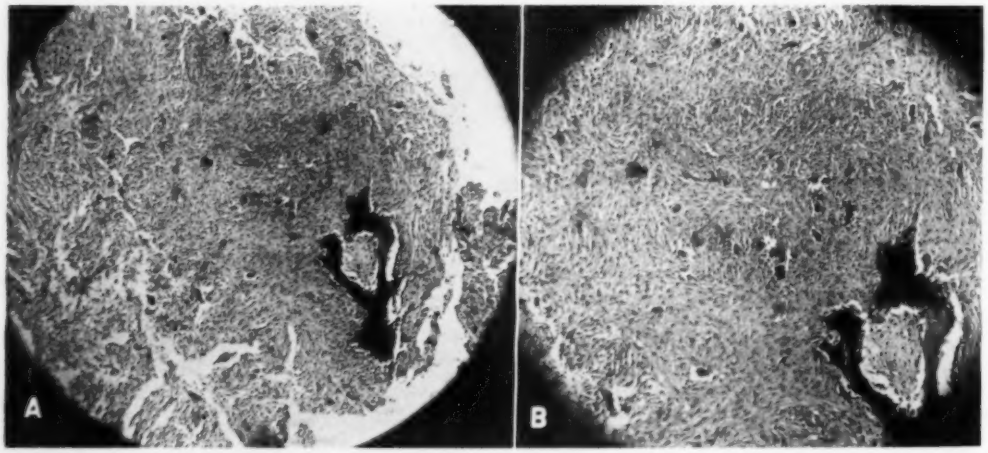


Fig. 5. Photomicrographs of a section from mandibular biopsy.
A. Low-power view, showing whorls of fibrous tissue adjacent to bony trabeculae.
B. Higher-power view demonstrating the fairly uniform character of the fibrous tissue cells, and the multiple scattered giant cells.

The pathologic diagnosis was "fibrous dysplasia of bone." After discussion with the Radiology Department, the findings were thought to be "consistent with familial multilocular cystic disease of bone."

It was noticed by one of us (O. S.) that

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Robert C. Brown, M.D.
3609 South Court
Palo Alto, Calif.

SUMARIO

Tumefacción Fibrosa Familiar de las Mandíbulas: Un Caso Nuevo

Preséntase un caso, que parece ser el décimo descrito, de tumefacción fibrosa familiar de las mandíbulas, la dolencia descrita por primera vez por Jones. El enfermo era un niño de cinco años, cuyos padre y tío comunicaron una historia y hallazgos indicativos de un proceso semejante en su juventud.

Aunque el examen microscópico de tejido biópsico procedente de la mandíbula reveló hallazgos típicos de displasia fibrosa, la aparente ocurrencia familiar y la naturaleza difusa del proceso en ambos maxilares indican que este caso es otro más de "tumefacción fibrosa familiar de las mandíbulas."

SUMARIO

Visualización de las Arterias Basilar, Cerebelosas y Vertebrales Durante la Angiografía Cerebro-Carótida
(*Pagina 738*)

Descríbense 3 casos en que se visualizaron los vasos arteriales de la fosa craneal posterior en el transcurso de la angiografía percutánea de las carótidas. En 1 caso, esto fué incidente a una trombosis de la carótida interna. En los otros 2, el medio de contraste atravesó la arteria comunicante posterior penetrando en las arterias cerebelosa superior y basilar.

Repásase la literatura.

The Button Sequestrum of Eosinophilic Granuloma of the Skull[1]

COL. PAUL O. WELLS, M.C.

THE SKULL IS one of the most common sites of eosinophilic granuloma of bone. Among the many articles which describe this lesion, however, only one (2) has specifically called attention to the rather characteristic sequestrum produced in some of these cases. This sequestrum appears as a "button" of intact bone in the center of a circular area of destruction. This finding has been noted roentgenographically by the author in 4 cases, all of which proved on histologic examination to be eosinophilic granuloma.

Fig. 1. Case I. Lesion in the occipital bone. Note the central sequestrum.

The patients 4 males in their early thirties, complained of a tender or painful area in the scalp, sometimes associated with headache or dizziness. Findings based on physical examination and laboratory studies were generally normal, except for an eosinophilia of 9 per cent in one patient and 8 per cent in another. A lesion or bone defect with a central sequestrum was revealed on the roentgenogram in each instance (Figs. 1–4).

Fig. 2. Case II. The osteolytic lesion in the right parietal bone involves both tables of the calvarium and contains a "button" of bone.

The roentgenographic picture is similar to that of osteomyelitis, and the histologic appearance is that of granulomatous tissue. The lesion develops in the diploe and characteristically destroys both tables of the calvarium without causing significant reaction in the adjacent bone. There is no expansion of the bone or periosteal new bone formation in the skull, in contrast to the lesions of eosinophilic granuloma seen in the long bones, where these changes are not uncommon.

Differential diagnosis is considerably simplified when the "button" sequestrum is observed in the lesion. Pyogenic osteomyelitis generally has a more "moth-eaten" aspect, with associated reaction in the adjacent bone, and is commonly found adjacent to an infected paranasal sinus or at the site of a previous craniot-

[1] From Letterman Army Hospital, San Francisco, Calif. Accepted for publication in November 1955.

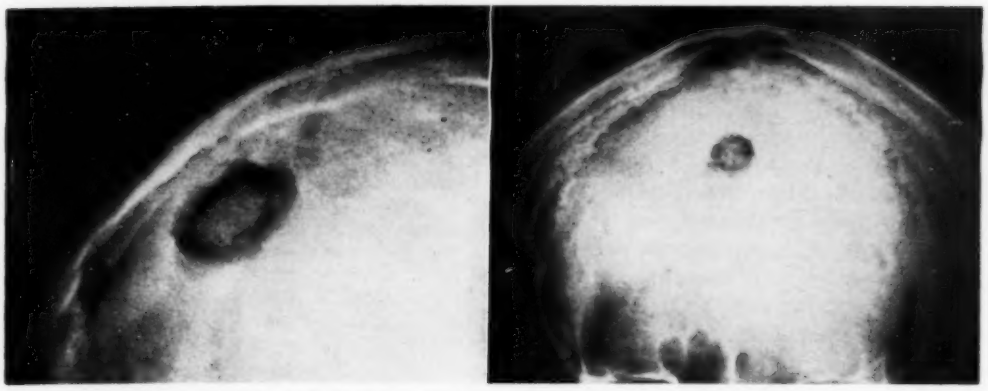

Fig. 3. Case III. Destructive lesion in the parietal bone with sequestrum but no reaction in surrounding bone.
Fig. 4. Case IV. Destructive lesion in the frontal bone with a central disk-shaped sequestrum.

omy or fracture. The possibility of syphilitic or tuberculous involvement must also be considered in spite of their rarity. Tirona (3) describes lesions in the skull with sequestrum formation attributed to tuberculosis, which are essentially identical with those considered in the present report. Metastatic neoplastic lesions cause bone destruction, but without sequestra. Post-traumatic fibrous changes in the bone might produce a similar appearance on the roentgenogram. Epidermoids, commonly found in the skull, have an irregular border of increased density without associated sequestration.

Several excellent articles have appeared on eosinophilic granuloma of the skull, covering the historical background adequately. At least one report (1) contains an illustration showing a sequestrum in the lesion, but no reference is made to it in the text. In another article (2) sequestration is described in one of the cases presented. In general, text books and articles tend rather to emphasize the absence of sequestrum formation in eosinophilic granuloma. It is believed, however, to be of relatively common occurrence in lesions involving the skull.

The etiology of eosinophilic granuloma of bone remains unknown. A virus origin, a traumatic factor, and relationship to Hand-Schüller-Christian's disease and Letterer-Siwe's disease have been mentioned as etiologic possibilities.

SUMMARY

The occurrence of a central bone sequestrum as observed in 4 cases of eosinophilic granuloma of the skull is reported. This sequestrum resembles a "button" of bone, and its demonstration is considered to be of diagnostic importance.

Harlan Memorial Hospital
Harlan, Ky.

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SUMARIO

El Secuestro en "Botón" del Granuloma Eosinófilo del Cráneo

Descríbese el aspecto de un secuestro óseo central observado en 4 casos de granuloma eosinófilo del cráneo, comprobados histológicamente. El secuestro se parece a un "botón" de hueso intacto en el centro de una zona circular de destrucción. Cuando existe, puede revestir importancia en el diagnóstico diferencial.

Pantopaque Pulmonary Embolism[1]

THEODORE E. KEATS, M.D.

PANTOPAQUE pulmonary embolus is an unusual complication of myelography. Review of the literature revealed 4 cases of venous intravasation during this procedure (1–4), with evidence of pulmonary embolization in only 2 of them (3, 4). We are presenting here an additional case of venous intravasation of Pantopaque during myelography, with demonstration of the opaque medium in both lungs.

B. G., a 32-year-old white female, was admitted to the University of California Hospital on May 22, 1955, complaining of pain in the left shoulder of two years duration. There was no history of trauma to this area. For the past year, there had been radiation of pain down the left arm, with paresthesia in the ulnar distribution. Three months prior to admission, dysphagia of a progressive nature developed.

The only abnormal physical findings were an area of tenderness to deep palpation in the left posterior cervical triangle, adiadokokinesis of the left hand, weakness of the left triceps and wrist extensors, possibly due to pain, absence of abdominal reflexes, and difficulty in balancing on the left foot.

Roentgen examination of the skull disclosed no evidence of disease. Moderate rotoscoliosis of the dorsal spine was present, with a minimal compensatory cervical scoliosis. The blood count was: 13.1 gm. hemoglobin, packed cell volume 39 c.c. per cent, white cells 5,600, with a normal differential count. The urine was normal.

Spinal puncture revealed clear, colorless fluid with a pressure of 80 mm. of water. The dynamics of the fluid with jugular compression were normal. Other cerebrospinal fluid findings were: no cells; Pandy test, 0; serology, negative; colloidal gold reaction, 0.0000000000.

On May 31, 1955, myelography was performed. Nine cubic centimeters of Pantopaque were injected into the lumbar subarachnoid space and the needle was removed. Under fluoroscopic observation, the oil was seen to pass from the caudal sac to the base of the skull in the prone and supine positions, without evidence of abnormality. The medium was then collected in the lumbar region in the prone position, in preparation for aspiration. Lumbar puncture was again performed and blood was obtained on aspiration. During this procedure, the patient experienced an episode of violent, uncontrollable coughing. Upon re-examination of the lumbar region fluoroscopically, only about 1.0 c.c. of oil was found to be present. Also noted, on either side of the remaining subarachnoid oil collection, were unusual strand-like extensions of the oil column, presumably within venous channels. Further attempts at aspiration were abandoned, and chest films were made immediately. These showed a finely granular pattern in both lower lung fields, particularly in the costophrenic sulci. The appearance suggested pulmonary embolization of the intravasated iodized oil (Fig. 1).

The patient continued to cough for approximately thirty minutes but experienced no other signs or symptoms until that evening, when her temperature rose to 37.4° C. The following day it reached 38.2° and on the third day 38.6°, with return to normal on the fourth day.

Roentgenograms of the chest made on July 19, 1955, forty-nine days after myelography, showed no evidence of embolized oil in the lungs (Fig. 2, A and B).

The patient was subsequently subjected to left scalenotomy, brachial plexus neurolysis, and left thoracoplasty with removal of the first and second ribs on the left. On Aug. 26, 1955, she was discharged from the hospital, improved.

When one considers the marked vascularity of the spinal canal, it is surprising that venous intravasation does not occur more frequently, particularly with the current wide use of opaque myelography. The pressure of the cerebrospinal fluid is higher than the pressure in the vertebral venous system, and any communication between the two would force fluid into the venous system. The rich internal venous plexus of the spinal canal communicates eventually with the inferior vena cava *via* the lumbar and lateral sacral veins, and thus with the lungs.

Steinbach (3) has estimated that, for roentgen visualization of the lungs, between 4.0 and 7.5 c.c. of Pantopaque must enter the venous system. In this case approximately 1.0 c.c. of the medium remained in the spinal canal. Roentgeno-

[1] From the Department of Radiology, University of California School of Medicine, San Francisco, Calif. Accepted for publication in January 1956.

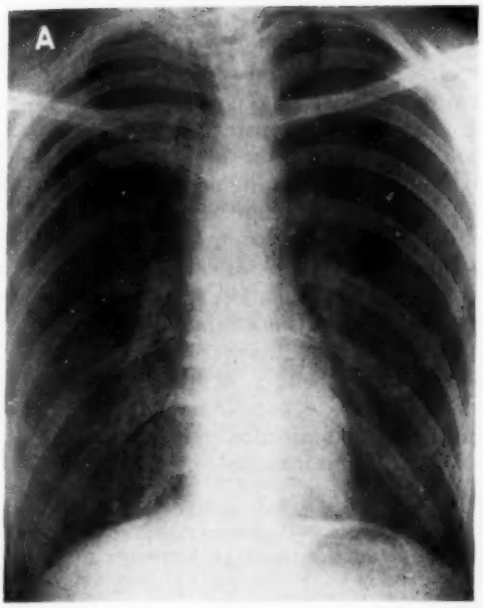

Fig. 1. A. Roentgenogram of the chest showing finely granular pattern of both lower lung fields representing embolized Pantopaque.
B. Enlarged roentgenogram of the right base demonstrating oil droplets to better advantage.

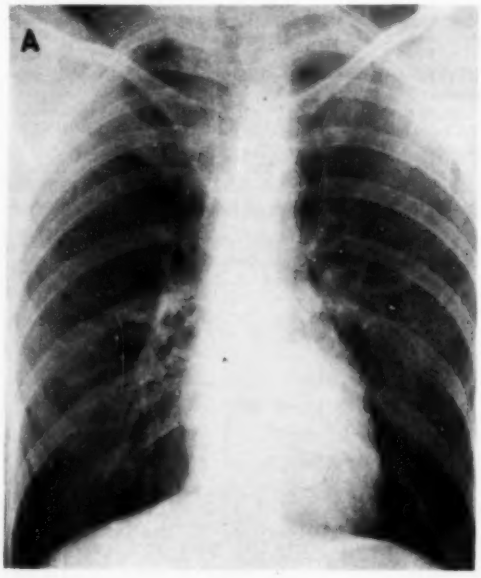

Fig. 2. A. Roentgenogram of the chest made forty-nine days after films of Fig. 1, showing disappearance of the oil droplets.
B. Enlarged roentgenogram of the right base for comparison with Fig. 1B.

grams of the material aspirated at myelography showed droplets of oil scattered throughout the clotted blood. The amount of this oil was estimated to be about 1.0 c.c. It appears, then, that the pulmonary embolization in this case amounted to approximately 7.0 c.c. This was immediately demonstrable in the lungs, and the opacity was therefore apparently due solely to the contrast material, with little associated pulmonary reaction.

Chest pain, non-productive cough, and fever are the common symptoms of Pantopaque embolism. Fat or oil embolism does not necessarily lead to pulmonary infarction, and this has been true in the other reported cases of patients with Pantopaque embolism. Sicard and Forestier (5) slowly injected 2.0 to 4.0 c.c. of Lipiodol intravenously into the cubital vein in man. Serial chest roentgenograms showed droplets of oil within the lungs for six to eight minutes, after which the oil suddenly disappeared, with no evidence of pulmonary infarction.

Gunn (6) has stated that fat embolism does not produce pulmonary infarction because of the small size of the globules which are filtered out into the capillaries and arterioles. Patchy hyperemia and edema are the only recognizable changes in the lung, except for stuffing of numerous small blood vessels with oil or fat. Death, in fat embolism, is the result of escape of globules from the pulmonary filter and passage to the vital centers of the brain.

SUMMARY AND CONCLUSIONS

A case of pulmonary Pantopaque embolism secondary to myelography has been presented. This is the fifth case of venous intravasation of Pantopaque after myelography to be reported, and the third instance of demonstration of the embolized oil within the lungs. The patient exhibited violent coughing at the time of embolization. Except for a febrile episode which lasted several days, she showed no complication from the embolism.

Venous intravasation may occur either during the injection of the opaque medium or during its aspiration. The aspiration of blood during either of these procedures should indicate temporary postponement of the examination to prevent passage of the contrast material into the venous system.

NOTE: The author wishes to express his appreciation to the Department of Neurosurgery of the University of California School of Medicine for the clinical data used in this paper.

Department of Radiology
University of Missouri College of Medicine
Columbia, Mo.

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SUMARIO

Embolia Pulmonar por Pantopaque

Preséntase un caso de embolia pulmonar por Pantopaque, secundario a la mielografía. La enferma experimentó un acceso violento de tos en el momento de la embolización. Aparte de fiebre que duró varios días, no hubo complicaciones debidas a la embolia.

La intravasación venosa puede ocurrir mientras se introduce el medio opaco o durante la extracción de éste. La aspiración de sangre durante uno u otro procedimiento debe indicar el abandono temporal del examen para impedir el paso de la substancia de contraste al sistema venoso.

Aplasia of the Lung

A Case Report[1]

HOWARD A. STEINER, M.D.

APLASIA AND agenesis of the lung are rare conditions, as indicated by a review of the literature. The term "agenesis" has been used to include pulmonary anomalies ranging from complete absence of a lung with its main bronchus to the condition in which a rudimentary bronchus and varying amounts of pulmonary tissue are present. The latter condition is more accurately referred to as "aplasia" of the lung.

Schneider (1) recognized three major types of congenital pulmonary defects: (*a*) true agenesis, with no trace of the lung, bronchus, or vascular supply on the affected side; (*b*) a rudimentary bronchus without pulmonary tissue (2); (*c*) a bronchus with varying amounts of pulmonary alveolar tissue extending from it. The case presented in this article is of the third type.

The diagnosis of aplasia or agenesis of the lung is made by roentgenographic, bronchoscopic, and bronchographic examination. Incomplete or total absence of aeration on the affected side of the thorax is noted on the roentgenogram. Flattening of the thorax on that side, with narrowing of the intercostal spaces and elevation of the diaphragm may also be seen. In a large percentage of the patients, additional congenital anomalies are demonstrated roentgenographically. These include accessory rudimentary ribs, hemivertebrae, and other vertebral irregularities.

While aplasia of the lung may be suspected from the roentgen appearances, certain conditions must be excluded, as pulmonary atelectasis, a plugged bronchus, tumor, bronchiectasis, and tuberculous stricture. For this reason, aid from the bronchoscopist is essential.

With the increased use of bronchoscopy and bronchography, aplasia or agenesis is diagnosed with increasing frequency. Burger (3) collected 54 cases in 1947, and Wexels (4) increased the number to 87 in 1951, which would suggest that the total may by this time be well in excess of 100.

Aplasia or agenesis is not incompatible with life, for there are on record patients ranging in age from the late fifties to seventy-two, who have died from other causes. In almost 50 per cent of the cases from the literature, however, death has occurred in the first five years of life, generally from infection. These patients do not tolerate respiratory infections well, and bronchopulmonary disease tends to be serious.

On bronchoscopic examination there may be slight deviation of the trachea toward the affected side. As a rule, the bronchial tree is clean and dry and, particularly in a newborn infant, there may be little or no secretion for aspiration. The bronchographic picture varies from complete absence of the main bronchus with no tracheal bifurcation to a rudimentary bronchus with or without alveolar tissue.

CASE REPORT

A white male infant, born Nov. 20, 1955, weighing 6 pounds and 5 ounces, appeared slightly cyanotic at birth but breathed spontaneously following routine aspiration. The mother, aged twenty-five, gave a history of a previous pregnancy terminating in the delivery of a normal female eighteen months earlier.

Twelve hours after birth, respirations became labored, cyanosis increased, and the patient was placed in an oxygen crib. Administration of penicillin, 10,000 units every three hours, was begun on the second day. A roentgenogram at that time (Fig. 1) revealed absence of aerated lung on the right, elevation of the right diaphragm, and flattening of the right hemithorax, with narrowing of the intercostal spaces. The left lung field was clear.

On the third day of life bronchoscopy was performed. No mucus was seen, and none could be as-

[1] From Sharon General Hospital, Sharon, Penna. Accepted for publication in January 1956.

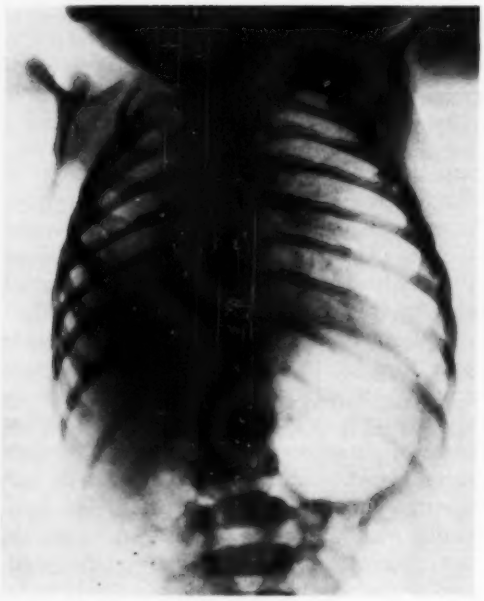

Fig. 1. Chest film taken on the second day of life, showing diminished aeration in the right lung field, with elevation of the right diaphragm and flattening of the right hemithorax.

Fig. 2. Bronchogram revealing a short, narrow right main bronchus terminating in a small amount of alveolar tissue. The left lung field appears normal.

pirated. The trachea deviated toward the right; the left main bronchus appeared normal. The right main bronchus could not be entered.

Fig. 3. Chest film taken on the sixteenth day of life. No aeration in the right lung field. Mottling about the left hilus, extending into the left lung field, is due to residual opaque oil (Lipiodol).

The child's condition remained critical, and on his removal from the oxygen crib the cyanosis became severe. It was noted, also, that respirations were more labored when he lay on the left side.

On the fifth day bronchography was attempted but was unsatisfactory, since the oil entered the esophagus. On the ninth day a second attempt was made. The baby was supported on a pillow at a 40° angle. The larynx was exposed with a flat laryngoscope, and under direct vision, a small, pliable silver cannula was introduced into the trachea. About 4 c.c. of Lipiodol was instilled, and a film was taken immediately (Fig. 2) revealing a short, narrow right main bronchus, terminating in a small amount of alveolar tissue; the eparterial branch was absent.

Normally the right main bronchus is larger than the left, in the proportion of 100 to 78.4, and it has a more vertical course (5). The angle which it forms with the median plane averages 24.8° as compared with an angle of 45.6° formed by the left bronchus. In the present case these relations were seen to be disturbed. The right bronchus formed an angle of approximately 22° and the left bronchus an angle of 25°, making it easier than usual for the bronchoscope to enter the left bronchus. The right diaphragm was elevated and the intercostal spaces of the right hemithorax were narrowed.

Beginning on the tenth day of life, the penicillin dosage was raised to 150,000 units daily. The infant was removed from the oxygen crib for increasing periods. On discharge from the hospital on the

seventeenth day, the general appearance and color had improved and the patient appeared quite well. A film obtained on the sixteenth day of life (Fig. 3), revealed residual opaque oil in the left lung field as evidenced by mottled opacities about the left hilus. No aeration was apparent in the right lung field.

The patient was readmitted to the hospital Dec. 27, 1955, and died the same day. The autopsy report reads: "The right lung is represented by a golf-ball-sized mass of grayish-white tissue arising from the right main bronchus. The tissue is posterior to the heart and is not loculated. Microscopically there is an island of air-containing tissue in the inferior portion of the right lung. The left lung is voluminous and emphysematous."

SUMMARY

A case of aplasia of the right lung in a newborn infant, with autopsy confirmation, is reported. The diagnosis was made by bronchography, which revealed a short, narrow bronchus terminating in a small amount of alveolar tissue. This condition is distinguished from true agenesis, in which there is no trace of lung, bronchus, or vascular supply on the affected side.

NOTE: The author wishes to express his appreciation to the following physicians of Sharon, for their cooperation in the compilation of the data for this case report: Dr. Dan Phythyon, obstetrician; Dr. Don H. Walker, otolaryngologist; Dr. Benjamin Wood, pediatrician.

291 Buhl Blvd.
Sharon, Penna.

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SUMARIO

Aplasia del Pulmón. Presentación de Un Caso

Se comunica un caso de aplasia del pulmón derecho en un recién nacido, con confirmación en la autopsia. El diagnóstico se hizo con la broncografía, que reveló un bronquio estrecho y corto que terminaba en una pequeña zona de tejido alveolar. Esta dolencia se diferencia de la verdadera agenesia, en la que no existen indicios de pulmón, bronquio o riego vascular en el lado afectado.

The Esophageal-Pleural Stripe on Chest Teleroentgenograms[1]

CHRISTIAN V. CIMMINO, M.D., F.F.R.[2]

SOME YEARS AGO, during study of a patient with upper thoracic pain, there was observed on the postero-anterior chest film a sickle-like shadow of soft-tissue density about 3 mm. thick and 30 mm. long, with the concavity to the right, just above the level of the clavicles, superimposed directly upon the gas shadow of the trachea (Fig. 1). Its nature was not known at that time. Over the years we have noticed it more and more frequently, which we attribute not only to our interest in it but also to our tendency to employ higher voltages, resulting in films of longer scale contrast. We have consulted several radiologists (1, 2) of wide experience about the nature of this shadow or stripe and, since it was new to them, it seemed advisable to report our observations.

Fig. 1. Soft-tissue stripe at and just above the level of the clavicles.

Nature: The left border of the stripe is perfectly demarcated by barium within the resting esophagus (Fig. 2). When the esophagus is functioning, however, the stripe may be lost (Fig. 3). It is usually continuous with the curve of the right apex of the lung, projected medially and downward. Its thickness varies from a barely preceptible hair-line to 3 or 4 mm. Since the entire right border of the thoracic esophagus is in direct contact with the right mediastinal pleura, and since the stripe follows exactly the course of the barium-filled esophagus (at least in its resting state), it is our belief that this shadow represents the mediastinal (parietal) and visceral pleura with any intervening capillary fluid, in addition to the major component, the right esophageal wall, which varies in thickness according to its functional state (Fig. 5).

Professor Folke Knutsson, who was consulted as to the nature of the shadow, is in complete agreement with this interpretation. Knutsson's paper (3) has some interesting anatomic details about the mediastinum *in vivo*, as revealed by transverse axial laminagraphy, and the reader is referred to it for sound anatomic knowledge of this region. Knutsson also called to our attention a monograph by Gladnikoff (4), in which this stripe is thoroughly considered, anatomically and radiographically. Gladnikoff, however, worked with a Lysholm grid and a film-focus distance of 0.5 mm., and his consideration of the stripe was only incidental to the roentgenographic study of the mediastinum in health and in primary pulmonary carcinoma. With his technic (relatively high voltage), he could often see the left wall of the esophagus as well as the right. We have not been able to do this.

The stripe as it appears on chest films has been dealt with by Danelius (5), among others (4), but he erroneously interpreted

[1] Accepted for publication in February 1956.
[2] Associate Professor of Clinical Radiology, Medical College of Virginia.

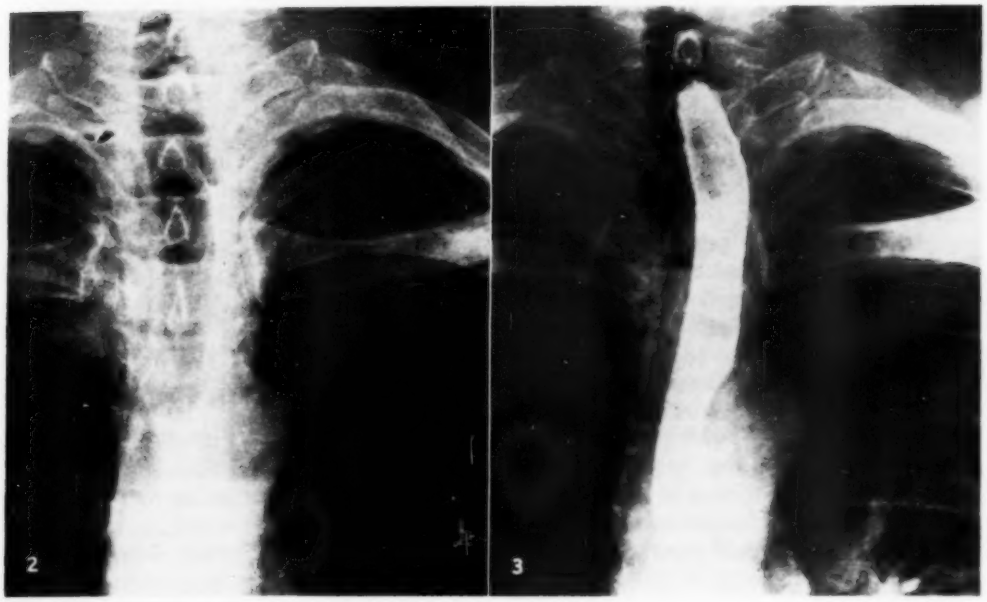

Fig. 2. The lumen of the esophagus as visualized with barium follows exactly the left border of the stripe. The esophagus is resting.
Fig. 3. Loss of the stripe with the esophagus at work.

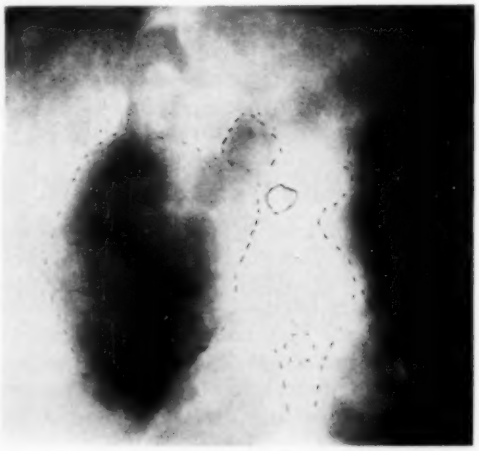

Fig. 4. Transverse axial tomogram, level of T 3 (retouched). Resting esophagus marked with barium. The mediastinal relationships may differ somewhat from those in the cadaver. Even in the living subject such relationships must vary with habitus, position, the point in the cardiorespiratory cycle, and the functional state of the esophagus.

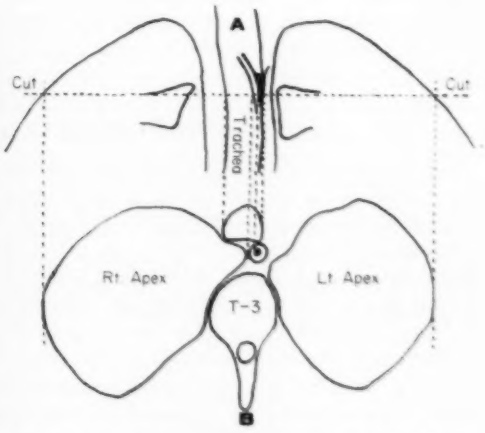

Fig. 5. A. Diagrammatic representation of stripe as seen in Fig. 2. B. Transverse section of A at level indicated, looking cephalad, constructed with the aid of Fig. 4.

it as thickened retro-esophageal pleura. With the spot-film equipment at hand at the time of his report, he was unable to distinguish the stripe from barium within the folds of the esophagus.

Incidence: The incidence of this shadow was studied statistically on 200 consecutive 6-foot postero-anterior chest films, the only criterion for inclusion being technical

perfection. It was found to occur in a statistically significantly greater number of children than adults, being observed in 18 of 185 adults, and 7 of 15 children. (The division between adulthood and childhood was taken at fifteen years, the level of significance at 3 sigmas.)

Significance: While the stripe is in no sense diagnostic, its presence on 6-foot chest films should be more widely known, especially since the trend is toward higher voltages, if only to avoid error in imputing pathologic significance to it. We have seen an occasional case in which the sickle was considerably thickened, due probably to inflammatory thickening of the right mediastinal and visceral pleura adjacent to the esophagus in this region. Small, relatively immobile accumulations of fluid and small tumors would produce the same picture.

SUMMARY

1. A sickle-like soft-tissue shadow is at times seen projected over the air column of the trachea at the level of the clavicles, with concavity to the right. It probably represents simply the right esophageal wall and its adjacent pleural covering.

2. It is not abnormal.

3. It was found in 25 of a consecutive series of 200 chest examinations. Its greater incidence in children as compared with adults is statistically significant.

NOTE: I wish to express my thanks to Dr. Mario Guttadauro, *Assistente, Istituto di Radiologia*, University of Rome, Italy, for his kindness in furnishing me with Figure 4.

I also thank Dr. H. C. Carter, Professor of Mathematics at the Mary Washington College of the University of Virginia, for the statistical analysis.

Mary Washington Hospital
Fredericksburg, Va.

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SUMARIO

Estría Esófago-Pleural en las Telerradiografías Torácicas

En las telerradiografías postero-anteriores del tórax obsérvase a veces una sombra falciforme de tejido blando, sobrepuesta a la sombra gaseosa de la tráquea, a la altura de las clavículas, con la convexidad a la derecha. Esto se descubrió 21 veces en una serie consecutiva de 200 radiografías torácicas.

Esta sombra no es anormal y no posee importancia diacrítica, representando probablemente la pared derecha del esófago y su adyacente revestimiento pleural.

EDITORIAL

Grid Therapy: An Evaluation

With x-rays in the 200- to 400-kv range, the healing process of radiodermatitis is one of the major limiting factors in treatment. Irradiation through a grid was first described by Köhler in 1909 as a method of protecting against radiodermatitis during administration of a tumor dose in depth. Although several modifications were subsequently suggested, the method did not gain favor until 1950, when Marks claimed complete healing of the skin after grid doses as high as 24,000 r. Such a claim offered a challenge to radiotherapists and stimulated a thorough physical and clinical investigation.

The grid is made of lead rubber with regularly spaced openings of small size relative to the dimensions of the field to be irradiated. The shape of the openings, whether square, round, or otherwise, is of little consequence, the important factor being the fraction of the irradiated area which is exposed, generally about 40 per cent. The principle is the maintenance of the grid pattern on the skin throughout the entire course of therapy, not so much to irradiate through the same openings as to preserve the areas covered by the grid to serve as centers of epithelial regeneration during the healing phase of the radiation reaction. In a single treatment, the grid pattern of maximum and minimum dosage exists throughout the irradiated volume of tissue even to the exit dose, with some slight blurring due to involuntary movements of the patient, as in respiration. In subsequent treatments, however, while the grid pattern on the skin can be reproduced more or less accurately, the slight but unavoidable shifts in direction of the x-ray beam or position of the patient make impossible an exact reproduction of the pattern in depth. In a course of therapy, therefore, in which many treatments are administered over a period of several weeks, the grid pattern in depth is practically obliterated and the depth doses are calculated as weighted averages.

With a 40 per cent open grid, the dose in the open areas must be approximately 2.5 times the conventional x-ray dose if equivalent depth doses are to be achieved. The skin reactions are very intense in the open areas. Nevertheless, the healing process is effective for grid doses as high as 12,000 r, administered over a period of four weeks, which appears to be the optimal maximum. With still higher amounts recovery may also occur, but the severe radiodermatitis prolongs the healing time to three or four months, with the added risk of radionecrosis.

In healing, the characteristic grid pattern is maintained, but months or years later the skin undergoes atrophy, telangiectasia, and scarring. It is probable that the columns of radiation through the open areas destroy the skin and the first 3 or 4 cm. of underlying tissue before the grid pattern is obliterated by the blurring effect. The destroyed tissue is absorbed and replaced by fibrosis from the intervening protected columns. After the skin is healed, the subcutaneous tissues gradually undergo contraction, distortion, and irregular thickening. The healing properties of these heavily irradiated tissues are poor, and any form of trauma, including surgery, may precipitate radionecrosis.

The essential value of irradiation through a grid is that the total dose that can be delivered in depth through a single field is more than twice the amount possible with conventional x-ray, but only at the expense of permanent damage to the skin and intervening tissues. The severe skin

changes would not be a deterrent if cancer could be completely destroyed, but there are few locations in the body where the radiation injury to the intervening tissues is tolerable.

In the irradiation of cerebral neoplasms, grid therapy is contraindicated because of the severe damaging effect on normal brain tissue, which would negate any beneficial effect on the tumor. In advanced inoperable cancer of the mouth, pharynx, and cervical lymph nodes, it is sometimes possible to obtain reduction of tumor masses, healing of ulcerations, and relief of symptoms with grid therapy even though the irregular surface of the neck makes reproduction of the grid pattern difficult. In cancer of the lung and cancer of the esophagus, high dosage with grid therapy is limited by radiation fibrosis of the lung or radiation myelitis of the spinal cord, either of which may be fatal if enough radiation is given to cause reduction in size of the tumor. A favorable exception is cancer involving only an upper lung field, for which reduction can be obtained with a limited amount of radiation fibrosis that does not cause crippling symptoms. Large doses to the spinal cord can be avoided by careful adjustment of the posterior field.

In the abdomen, grid therapy is contraindicated because of the risk of intestinal perforation with peritonitis or fistula formation, especially in the region of operative scars, where adhesions are likely. The grid may be usefully employed, however, for advanced inoperable cancer of the bladder, because there are not likely to be any loops of intestine between the skin of the suprapubic area and that organ. A contraindication is an inguinal hernia, unless it is easily reducible. Another contraindication is a thick adipose panniculus. Fatty tissues do not heal well, particularly where there are folds of skin, as in the lower abdomen and groins. In advanced cancer of the cervix or corpus uteri for which radium therapy cannot be adequately applied, a limited degree of palliation can sometimes be achieved with grid therapy. On the other hand, advanced cancer of the ovary is not suitable for such treatment, because of its mode of spread in the peritoneal cavity. Grid therapy to high dosage may sometimes be usefully applied to single large tumors that are relatively superficial in location, provided there are no radiosensitive intervening structures. An example of such a tumor is a fibrosarcoma of the pelvic wall, which can be treated through the muscular tissues of the buttock.

Grid therapy is frequently compared to supervoltage therapy because both are methods of administering a large tumor dose through a single field. At this point, however, the comparison ends, since the severe effects of grid therapy on the skin and subcutaneous tissues are in marked contrast to the relatively slight reactions which occur after high dosage with supervoltage radiation, nor does grid therapy possess other advantages of supervoltage radiation, such as diminished bone absorption, better depth dose, and less side-scatter.

In general, grid therapy is limited to those situations in which the damage to normal tissues does not produce a condition worse than the original disease, such as the complications of brain or spinal cord injury, the cough and dyspnea of pulmonary radiation fibrosis, the risks of intestinal perforation, or the suffering of radionecrosis. Much useful palliation can be achieved in some cases of advanced cancer of the head and neck, in upper lobe cancer of the lung, in bladder and uterine cancer, and in peripherally situated tumors. For the majority of radiotherapists who have 200- to 400-kv radiation at their disposal, grid therapy is a useful method of achieving such palliation

SIDNEY M. SILVERSTONE, M.D.

ANNOUNCEMENTS AND BOOK REVIEWS

BROOKLYN RADIOLOGICAL SOCIETY

At a recent meeting of the Brooklyn Radiological Society the following officers were elected for the ensuing year: President, Dr. Daniel G. Butera; Vice-President, Dr. Theodore Kamholtz; Secretary-Treasurer, Dr. Harold N. Schwinger, 62 Eighth Ave., Brooklyn, N. Y.

KINGS COUNTY RADIOLOGICAL SOCIETY

Newly elected officers of the Kings County Radiological Society are: Sol Maranov, M.D., President; Aaron Tolk, M.D., Vice-President; Ernest I. Melton, M.D., 2187 Ocean Ave., Brooklyn 29, N. Y., Secretary-Treasurer.

MINNESOTA RADIOLOGICAL SOCIETY

The following officers have been elected by the Minnesota Radiological Society for the coming year: A. L. Abraham, M.D., Duluth, President; David G. Pugh, M.D., Rochester, Vice-President; O. J. Baggenstoss, M.D., 1953 Medical Arts Building, Minneapolis 2, Minn., Secretary-Treasurer.

NORTH CAROLINA RADIOLOGICAL SOCIETY

At a recent meeting of the North Carolina Radiological Society, the following members were elected to office: President, Dr. James S. Raper, Asheville; President-Elect, Dr. Waldemar C. A. Sternbergh, Charlotte; Vice-President, Dr. John Wear, Salisbury; Secretary-Treasurer, Dr. William Sprunt, Department of Radiology, North Carolina Memorial Hospital, Chapel Hill, N. C.

SAN FRANCISCO RADIOLOGICAL SOCIETY

Officers of the San Francisco Radiological Society, recently elected, are: Tom M. Fullenlove, M.D., President; Harold Hill, M.D., President-Elect; Gordon King, M.D., Member of Executive Board; Irma Smith, M.D., 450 Sutter St., San Francisco 8, Calif., Secretary-Treasurer.

COURSE IN OPERATIVE RADIUM THERAPY QUEENS GENERAL HOSPITAL

A course in Operative Radium Therapy will be offered at the Queens General Hospital by the Radiation Therapy Department, beginning Saturday, Jan. 5, 1957, and extending for eight consecutive Saturdays from 9 A.M. until 12 noon. The program will cover interstitial irradiation in the oral cavity, radical insertion of radium in the neck, radium therapy in postoperative carcinoma of the breast, the use of different applicators in carcinoma of the cervix, the Heyman applicator in carcinoma of the endometrium, radium needle implantation in the parametria, and radon, iridium-thread, and interstitial cobalt therapy.

Application may be made to Dr. L. B. Goldman, Director, Department of Radiation Therapy, Queens General Hospital, 82-68 164th St., Jamaica 32, N. Y.

FIFTH SYMPOSIUM NEURORADIOLOGICUM

The Fifth Symposium Neuroradiologicum is being held in Brussels from July 21 to July 26, 1957, as an integral part of the First International Congress of Neurological Sciences. Papers for presentation and contributions to the Scientific Exhibit are invited. Further information may be obtained from Professor G. J. Melot, Service de Radiodiagnostic, Hôpital Universitaire St. Pierre, Brussels, Belgium.

RESEARCH GRANTS AMERICAN CANCER SOCIETY

The American Cancer Society is now prepared to receive applications from individual scientists and institutions for grants under its newly organized research program. Application forms may be obtained from the American Cancer Society, 521 West 57th St., New York 19, N. Y. Applications received before Jan. 1 will be acted upon during the late winter and early spring, and most grants will become effective July 1, 1957.

FELLOWSHIPS IN RADIOLOGICAL PHYSICS

The U. S. Atomic Energy Commission has made available a number of special fellowships in radiological physics for the academic year 1957–58. The program provides for an academic year of formal courses at one of four universities, followed by transfer to a corresponding co-operating AEC installation for approximately three months training in applied health physics. The four centers of the program are at the University of Rochester, in co-operation with Brookhaven National Laboratory; the University of Kansas and the University of Washington, in co-operation with the Hanford Works; and Vanderbilt University, in co-operation with Oak Ridge National Laboratory. Information as to requirements, financial arrangements, and other details, as

well as application blanks, may be obtained from the Fellowship Office, University Relations Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tenn. Completed applications, supporting letters of reference, and transcripts must reach the Institute not later than Feb. 15, 1957, to ensure consideration. Appointments will be made on or about March 15, 1957.

Books Received

Books received are acknowledged under this heading, and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

DISEASES OF THE HEART. By CHARLES K. FRIEDBURG, M.D., Attending Physician, The Mount Sinai Hospital, New York; Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. A volume of 1,162 pages, with 157 figures. Published by W. B. Saunders Co., Philadelphia and London, 2d ed., 1956. Price $18.00.

CLINICAL PATHOLOGY. APPLICATION AND INTERPRETATION. By BENJAMIN B. WELLS, M.D., Ph.D., Director of Clinical Investigation, The Lynn Clinic, Detroit, Mich.; Former Professor of Medicine and Chairman of the Department of Medicine, Creighton University School of Medicine, Omaha, Neb. A volume of 488 pages, with 25 figures and 32 tables. Published by W. B. Saunders Co., Philadelphia and London, 2d ed., 1956. Price $8.50.

PELVIMETRY. By HERBERT THOMS, M.D., Emeritus Professor of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Conn. A volume of 120 pages, with 45 figures and 4 tables. Published by Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., New York, 1956. Price $5.00.

PROGRESS IN RADIOBIOLOGY. Proceedings of the Fourth International Conference on Radiobiology held in Cambridge on 14th to 17th August 1955. Edited by JOSEPH S. MITCHELL, BARBARA E. HOLMES, and CYRIL L. SMITH, Department of Radiotherapeutics, University of Cambridge. A volume of 558 pages, with numerous figures and tables. Published by Charles C Thomas, Springfield, Ill., 1956. Price $12.75.

BASIC MECHANISMS IN RADIOBIOLOGY. IV. CELLULAR ASPECTS. Proceedings of an Informal Conference, Bear Mountain, New York, May 12–14, 1955. HARVEY M. PATT and E. L. POWERS, Editors. A report of 190 pages, with 14 figures and 2 tables. Publication 450, National Academy of Sciences, National Research Council, Washington, D. C., 1956. Price $1.75.

TWENTIETH SEMIANNUAL REPORT OF THE ATOMIC ENERGY COMMISSION. 260 pages. United States Government Printing Office, Washington D. C., July 1956.

THE MEDICAL ANNUAL. A YEAR BOOK OF TREATMENT AND PRACTITIONERS' INDEX. Editors: SIR HENRY TIDY, K.B.E., M.A., M.D. (Oxon), F.R.C.P., AND R. MILNES WALKER M. S. (Lond.), F.R.C.S. A volume of 548 pages. Published by John Wright & Sons Ltd., Bristol, and The Macmillan Co., of Canada, Ltd., Toronto, 1956.

DIE LUNGENTUBERKULOSE. DIAGNOSE UND THERAPIE. By Prof. Dr. Med. PAUL-GEORG SCHMIDT, Chefarzt der Westerwaldklinik Waldbreitbach, Tuberkulose-Krankenhaus der LVA Rheinprovinz. Third edition, completely revised. A volume of 384 pages, with 234 illustrations. Published by Georg Thieme Verlag, Stuttgart, 1956. Distributed in the United States and Canada by the Intercontinental Medical Book Corporation, New York, N.Y. Price DM 58—($13.80).

II^e CONGRÈS INTERNATIONAL DE RADIOPHOTOGRAPHIE MÉDICALE. PARIS—4–7 AVRIL 1956. RAPPORTS. A volume of 356 pages, with numerous figures and tables. Published by Masson et Cie, 120, Boulevard Saint-Germain, Paris-6^e, 1956. Price 2,500 fr.

Book Reviews

ORAL CANCER AND TUMORS OF THE JAWS. By GEORGE S. SHARP, M.D., F.A.C.S., F.A.C.R. (Ther.), Professor of Pathology, School of Dentistry, Assistant Clinical Professor of Surgery, School of Medicine, University of Southern California, Director, Pasadena Tumor Institute; WELDON K. BULLOCK, M.D., M.Sc. (Path.), Associate Clinical Professor of Pathology, School of Medicine, University of Southern California, Surgical Pathologist, Los Angeles County Hospital; and JOHN W. HAZLET, D.D.S., Lecturer, Oral Tumor Pathology, School of Dentistry, University of Southern California. A volume of 562 pages, with numerous illustrations, including roentgenograms. Published by McGraw-Hill Book Company, Inc., New York, 1956. Price $15.00.

Though the authors of this work on oral cancer are pathologists, they have not sought to produce a text book on the pathology of cancer or a guide to its management, but rather "a syllabus for the oral diagnostician" to aid the general pracitioner and the dentist in arriving at a differential diagnosis

of particular lesions by inspection and palpation prior to biopsy. The result is a valuable book, reflecting the wide experience of the writers and offering much to those who deal with lesions of the mouth and jaws in either their diagnostic or therapeutic aspects. It may well contribute to earlier diagnosis of lesions in this area.

The text is presented in five parts, *viz.*, (1) Introductory Principles for Neoplastic Diseases; (2) Benign and Malignant Tumors of the Oral Mucosa and Accessory Cavities; (3) Benign and Malignant Neoplasms of the Jaws; (4) Quasi-Tumors of the Jaws; (5) Cysts of the Jaws.

In dealing with lesions in the various areas, the gross anatomy of the region is first described. The incidence and etiology are then taken up, together with a description of the histopathology, clinical characteristics, treatment methods, prognosis, and differential diagnosis. The text is unusually well illustrated with photographs and appropriate roentgenograms. A short bibliography is given at the end of each chapter.

PRACTICE IN RADIOTHERAPY. Edited by SIR ERNEST ROCK CARLING, LL.D., F.R.C.S., F.R.C.P., F.F.R., Consulting Surgeon, Westminster Hospital; Chairman, International Commission on Radiological Protection; B. W. WINDEYER, M.B., B.S., D.Sc., F.R.C.S., F.R.A.C.S., F.F.R., Professor of Radiology, University of London; Director, Meyerstein Institute of Radiotherapy, Middlesex Hospital; Consultant in Radiotherapy to the Royal Air Force; and D. W. SMITHERS, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy, University of London; Director, Radiotherapy Department, Royal Cancer Hospital; Consultant in Radiotherapy to the Royal Navy. A volume of 550 pages, with 140 figures and numerous tables. Published by Butterworth & Co., Ltd., London, England, and C. V. Mosby Co., St. Louis, Mo., 1955. Price $20.00.

More than 50 contributors, including Great Britain's best known radiotherapists, many surgeons and gynecologists, and specialists in other fields have collaborated in producing this concise but comprehensive, well rounded text on radiotherapy. It will serve not only as a guide to the best management for a specific neoplastic situation, but also give the rationale for the choice.

Part I is concerned with general problems, as dosimetry, with reference to theory, instrumentation, and dosage in clinical practice; current concepts of the physical basis of action of radiation on living material and its biological effects; different methods of delivering radiation, as x-rays, radium, and isotopes, and the choice of one modality over another; treatment planning, and protection factors.

Part II, the clinical portion of the book, consists of sections devoted to practically all types of malignant disease as well as to non-malignant conditions commonly encountered by the radiotherapist. The clinical features of neoplastic diseases are well presented, and the standard of writing is high. Considering the varied authorship of this book, the different sections are surprisingly uniform in style, organization, and clarity.

One of the most important and timely features of this text is the discussion of radiation therapy versus surgery in the management of specific neoplasms. The sections are organized in such a way as to present the relative merits of different modes of management and the changing values of various methods as applied to neoplastic disease in different stages of its natural history. The indications for radiation therapy are clearly outlined. Although the conclusions may not be acceptable to all, the arguments are worthy of serious consideration.

Dose-time relationships are given well deserved attention, and methods and technics of irradiation are adequately described for those who are interested in a specific treatment plan. As one would expect, radium planning and management are emphasized. Most sections contain data on results, making the presentation more complete.

The last section, entitled "Records and Presentation of Results," stresses careful records and honest analysis and the accumulation of much valuable data as a basis for advancement of radiation therapy.

This excellent book should find a welcome in the library of the novice, the advanced radiotherapist, and, indeed, anyone interested in the management of cancer.

DIE RÖNTGENBILDANALYSE. EINE RÖNTGENDIAGNOSTISCHE ANLEITUNG FÜR STUDIERENDE UND ARZTE. By PROF. DR. ERICH SAUPE. Third Edition, newly revised by PROF. DR. W. TESCHENDORF, Köln. A volume of 284 pages, with 328 illustrations. Published by Georg Thieme Verlag, Stuttgart, 1956. Distributed in the United States and Canada by the Intercontinental Medical Book Corporation, New York, N. Y. Price DM 49.50 ($11.80).

This is the third edition of a text book purposefully aimed at the fundamentals of x-ray diagnosis. The opening chapter illustrates this by presenting the very rudiments of x-ray diagnosis without apology. The first heading is "Central Projection Particularly in Reference to the Inverse-Square Law." Then, following the matter of summation shadows, the analysis of ring shadows in the lung fields is considered. The frequently forgotten Mach effect and Ludloff's radiolucency are convincingly pictured. The importance of accurate beam direction and correct positioning is correlated with the roentgen anatomy of the lungs.

The greater part of the book, following this basic chapter, is taken up with the various body systems.

The individual items are numerous and frequently unrelated in other than a broad sense of protecting the radiologist against certain pitfalls. On the development of the skeleton, observations which are apt to confuse the student but which are well known to the more experienced receive attention. For example: block vertebrae, osteopoikilosis, Looser zones, fibrous dysplasia, and hemangioma are described. The most extensive description is accorded pulmonary tuberculosis. One of the finest reproductions in the text is that of a case of pericardial calcification.

The roentgen contrast procedures are given some space individually, but detailed discussion is not attempted. Both electrokymography and roentgenkymography, as well as the less commonly attempted arterial contrast studies are mentioned. Additional subjects include photoroentgenography, stereoscopy, and foreign-body localization.

Well bound and profusely illustrated with reproductions of excellent quality, this book should prove very useful to first and second year residents in radiology. The work should also be of value to any physician forced by circumstance to take a board examination in the general field of medicine. He could quickly scan the field of radiology by reading this text of less than three hundred pages.

In Memoriam

W. Warner Watkins, M.D.

W. WARNER WATKINS, M.D.

1883–1956

On April 10, 1956, Phoenix, Ariz., lost one of its most prominent citizens with the death of Dr. W. Warner Watkins. Dr. Watkins was born in Keysville, Va., in 1883 and received his preliminary education there. He was graduated from the Virginia Medical School and in 1906 received a license to practice medicine in Arizona, which at that time was still a territory. He served as the physician and surgeon of a mining camp near Metcalf for eighteen months and then moved to Phoenix.

While Director of St. Luke's Hospital in 1911, Dr. Watkins opened the first clinical and x-ray laboratory in the state of Arizona. In 1914, he established a private laboratory for pathology and radiology; in 1917, he became associated with Dr. H. B. Mills, who took charge of the department of pathology, allowing Dr. Watkins to devote his full time to radiology. In 1920, he organized radiological and pathological laboratories in both St. Joseph's and the Good Samaritan Hospitals.

Among his contributions to medicine were fixation tests for tuberculosis and research on leukocytes in that disease. He performed the first pneumothorax in Arizona (1912) and introduced Wassermann testing of all inmates of the State prisons and State hospitals. He was responsible also for roentgenographic and fluoroscopic examinations of all draftees from Arizona in World War I.

Dr. Watkins was an outstanding figure in the medicine of the Southwest. He aided in the reorganization of the County Medical Society in 1908 and later served as its Secretary and President; he served also as Secretary (1912–1913) and President (1918–1919) of the State Medical Society; he was a charter member of the Southwestern Medical Association, serving as Vice-President in 1919, President in 1920, and as Secretary for eleven years. In 1912, he assisted in the formation of the present Arizona Tuberculosis and Health Association. He was its President in 1914 and its Treasurer for twenty-five years. As a member of the Association for the Advancement of Science, he aided in the formation of its Southwestern Division.

The American College of Physicians granted him a Fellowship in 1921, with Life Membership in 1944; he held the office of Governor of the College for ten years. He was a member of the Radiological Society of North America, serving two terms as Vice-President. He belonged also to the American Roentgen Ray Society,and the American College of Radiology.

Dr. Watkins was an active member of the Baptist Church. He was for many years a member of the Board of Directors of the Local Y.M.C.A. and for two years its President. He served for twenty years as a member of the Board of Directors of the

Social Service Center, and for five years on the Board of Directors of the Urban League. He was for five years President of the Cook Christian Training School for Indians and was a member of the Phoenix Lions Club.

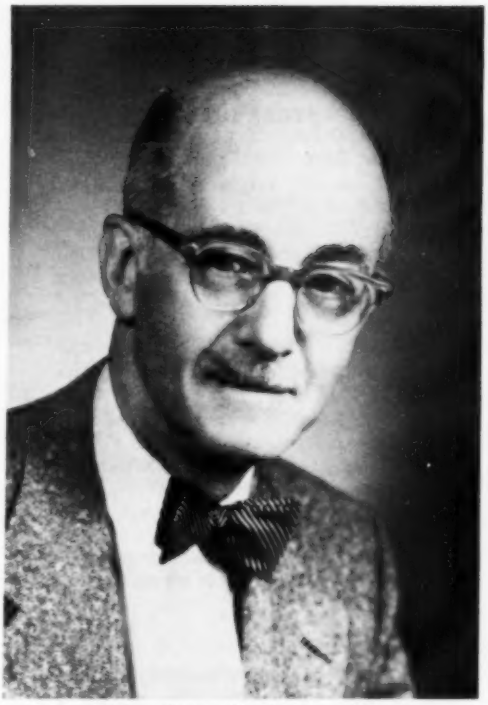
Dr. Watkins was a pioneer in Arizona medicine, an organizing force in medical and educational movements, and a leader in public health problems, serving with distinction in local, state, and national spheres. BENJAMIN H. ORNDOFF, M.D.

HARVEY NORTON MAWHINNEY, M.D.

1892–1956

Dr. Harvey Mawhinney, for nearly thirty years a member of the Radiological Society of North America, died on June 17, 1956. Dr. Mawhinney was born in Pittsburgh, Penna., in 1892, received his education in that city, and spent his professional life there. He was graduated from the Medical School of the University of Pittsburgh in 1920 and served his internship in Mercy Hospital. Upon completion of a residency in urology in that institution, he turned to radiology, serving a residency in Presbyterian Hospital, New York. In 1926 he returned to Mercy Hospital, with which he was associated until 1944, when he joined Drs. Zoe Johnston and Dr. Forrest L. Schumaker in the private practice of radiology. He was subsequently associated with Drs. Newton Hornick, Peter M. Feltwell, Jr., and Norman B. Tannehill. From 1942 to 1949 he was connected with the Medical Department of the Bell Telephone Company of Pennsylvania. At the time of his death he was roentgenologist on the staffs of Homestead Hospital, Homestead; Suburban General Hospital, Bellevue; and Ohio Valley General Hospital, McKees Rocks, Penna.

As a medical student, Dr. Mawhinney was active in the influenza epidemic at the time of World War I. In World War II, he served as a medical examiner on the local Induction Board. He was a fellow of the American College of Radiology and of the American Board of Radiology, and a member of the Pennsylvania and Pittsburgh Radiological Societies, both of which he had served as President.



Harvey Norton Mawhinney, M.D.

Dr. Mawhinney is survived by his wife, the former Louise Culley, and by two daughters, Mrs. Ross Jones and Mrs. William McCandless. His son, Harvey, Jr., died in 1954.

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ROENTGEN DIAGNOSIS

THE HEAD AND NECK

The Electroencephalogram in Head Injuries with Subdural Hematoma. Joseph G. Chusid and C. G. de Gutierrez-Mahoney. Neurology **6:** 11–21, January 1956. (145 W. 11th St., New York 11, N. Y.)

This article deals primarily with electroencephalography, performed in 55 patients with operatively confirmed subdural hematomas, either before or after surgery, or both. The results are discussed, but it is concluded that cerebral angiography is a more reliable and accurate test for the demonstration of supratentorial subdural hematomata in adults with head injuries. In the series reported, percutaneous carotid angiography disclosed the subdural hematoma in 6 of the 7 cases in which it was used. A characteristic pattern noted in the anteroposterior view during the arterial or capillary phase consisted of an avascular area subjacent to the cranial vault, usually with displacement of the anterior cerebral artery toward the opposite side. In the case in which angiography failed, the critical anteroposterior view was unsatisfactory.

Carotid angiography is much less likely than pneumography to disturb seriously the dynamics of a compromised ventricular system and brain such as may be associated with subdural hematoma.

Three roentgenograms; 2 photographs; 3 electroencephalograms; 4 tables.

Preliminary Note on the Study of Central Nervous System Lesions by Serial Stereoscopic Cerebral Angiography with Automatic Control. Jesús M. Sánchez-Pérez. Rev. mex. de radiol. **10:** 35–43, January-February 1956. (In Spanish) (Mexico 7, D.F., Mexico)

The author describes a device for serial stereoscopic cerebral angiography in which two transformers are coupled to twin rotating anode tubes, mounted side by side so that their focal spots, located in the same vertical and horizontal planes, are 9.5 cm. apart, centered over a seriographic device, also of his design (Surgery **13:** 661, 1943. Abst. in Radiology **41:** 598, 1943). After injection of 8 c.c. of Renografin (Squibb), six (three double) 0.10-second exposures, alternately from the twin tubes, are timed by the relays in the seriograph, so that an interval of seventy seconds is interposed between the second and the third, and the fourth and the fifth roentgenograms. The timing is based on the observation that contrast material will stay an average of four seconds in the cerebral circulation.

Four cases are illustrated: glioblastoma multiforme of the right parietal region, thrombosed aneurysm of the internal carotid artery, highly vascularized tumor in the right temporal fossa, and thrombosis of the left anterior cerebral artery.

Four double stereoroentgenograms; 1 photograph.

E. R. N. Grigg, M.D.
Cook County Hospital, Chicago

Obstruction of the Superior Longitudinal Sinus by Plasmocytoma. James Barr and Alex Daws. Brit. J. Surg. **43:** 372–374, January 1956. (The Royal Infirmary, Cardiff, Wales)

A case of multiple myeloma is presented, with involvement of the skull and intracranial extension causing obstruction of the sagittal sinus. The patient was thirty-two years of age, which is relatively young for this disease, and presented other confusing features. There was evidence of increased intracranial pressure and the roentgenogram showed a single irregular defect in the squamous occiput to the left of the mid-line, just above the external occipital protuberance.

The importance of the roentgen defect was not apparent until a fluctuant mass became palpable in this area. An occipital craniotomy was then done, with removal of tumor tissue extending intracranially as far medially as the superior sagittal sinus, which appeared then to be patent. The tumor proved histologically to be a plasmocytoma. Within a week all neurological signs were normal, but roentgen studies showed numerous small areas of destruction in the skull, as well as elsewhere in the skeleton, almost certainly myelomatous deposits. Marrow smear and plasma protein studies were also typical.

The patient did well for about two weeks, at the end of which time, severe neurological signs developed, followed promptly by death. Autopsy was not obtained, but it seems likely that there was an acute thrombosis of the sagittal sinus in the region of the tumor. Death was thought to be due to medullary failure, the result of a rapid rise in intracranial pressure.

One roentgenogram; 1 photomicrograph.

Zac F. Endress, M.D.
Pontiac, Mich.

Roentgenographic Changes in the Calvarium in Hypophyseal Tumors. W. Knittel. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 828–833, December 1955. (In German) (Universitätsnervenklinik Jena, Ob. Philosophenweg 3, Jena, Germany)

Among 82 cases of pituitary tumor reviewed by the author, 9 showed bony defects in the calvarium. The 3 cases showing the most marked changes are described in detail.

The bony lesions consisted of localized loss in bone substance very similar to that seen in metastatic carcinoma of the vault and in some cases of multiple myeloma. In 1 case the defects were first considered to be *foveolae granulares*, that is, the imprints of enlarged pacchionian bodies, and would have been dismissed as such except for their actual location and for the final autopsy studies. In all instances the foci of bone destruction were located in the vault itself, with a predilection for the frontal and temporal bones. Despite the original assumption that the lesions represented metastatic tumor, microscopic examination in all 9 cases showed only a localized osteoporosis with medullary fibrosis.

Speculation as to the cause of the lesions leads first to a consideration of increased intracranial pressure. Chronic increase in intracranial pressure can cause skull changes, but in most instances the changes involve the base. Several of the patients considered here had basophil adenomas, a notoriously slow-growing tumor and one not apt to cause true pressure symptoms. Roentgen injury can be ruled out because 2 of the patients showing rather definite lesions had received no irradiation. Direct pressure on the internal carotid artery also seems an unlikely cause. The author favors a hormonal influence. The two disease processes represented in the present series were basophil adenoma and

eosinophilic adenoma. Both of these are known to influence bone production. It must be noted that of the 9 patients with bone lesions 7 were females, although males predominated in the series as a whole.

Four roentgenograms.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Developmental Disturbances of the Atlanto-Occipital Junction. K. Decker, H. Fischgold, H. Hacker, and J. Metzger. Fortschr. a. d. Geb. d. Röntgenstrahlen **84:** 47–57, January 1956. (In German) (K. D., Nussbaumstrasse 7, München, Germany)

The authors carefully studied 45 cases of anomalies at the atlanto-occipital junction in order to evaluate their relationship to certain neurologic disorders. The question as to why some patients exhibit neurologic symptoms, while others with the same anomalies do not, still remains problematic.

The anomalies are divided into four groups. The largest of these comprised 21 cases of basilar impression and platybasia (herniation of the upper cervical spine into the posterior cranial fossa). The other three groups were, respectively, fusion of the atlas to the occipital bone (12 cases), accessory occipital vertebrae (4 cases), and anomalies of the odontoid process (8 cases). In every case careful x-ray examinations were carried out with special technics. A great deal of information was obtained from anteroposterior and lateral laminagrams taken during myelography after lumbar instillation of gas, which is the only method for determining the actual distance between the spinal cord and the anterior edge of the foramen magnum of the occipital bone. Encephalography and ventriculography were often done.

Of particular interest were the changes in the aqueduct, which was occluded in 2 cases and distorted in others, but the differential diagnosis between mechanical changes due to the anomaly and tumors could not always be made.

The relationship of the anatomical structures during movement was carefully studied, and the angle between the clivus and the odontoid process of the axis was measured. It could be shown that in any movement of the skull practically all joints of the upper cervical spine were involved. The fact that in some of the patients neurologic symptoms did not develop until late in life can be explained by the degenerative processes of advancing age in the upper cervical spine, with compression of the nerve structures. Movements of the head causing undue backward slipping of the odontoid process, and therefore narrowing of the foramen magnum and pressure upon the cord, could explain many of the neurologic symptoms. Particularly involved were the pyramidal tract and the anterolateral tracts for sensations of temperature and pain. The clinical findings resembled those of multiple sclerosis or syringomyelia.

It is not easy to establish a definite relationship between bony anomalies and neurologic symptoms. Associated with the osseous abnormalities there may be neurological malformations producing strictures of the aqueduct, disturbances of cerebrospinal fluid circulation, and certain clinical symptoms. Furthermore, the bony anomalies may be only incidental and the symptoms may be due to other disturbances, as chronic arachnoiditis, thickened bands of dura, or tumors. Ten per cent of the authors' patients had tumors.

Of the four groups of anomalies mentioned above, fusion of the atlas to the occipital bone led most often to neurological symptoms (over 80 per cent). For each of the other three groups the figure was only 50 per cent.

Pneumography was valuable in evaluating these cases; arteriography of the vertebral arteries, done in 20 per cent of the patients, seldom gave any worthwhile information.

Ten roentgenograms; 1 drawing.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Fibrous Dysplasia of the Mandible. Michael L. Lewin. Am. J. Surg. **90:** 951–961, December 1955. (67 E. 78th St. New York 21, N. Y.)

The author reviews briefly the general subject of fibrous dysplasia and presents the changing concepts of the disease. The radiologic appearances are dependent upon the histologic make-up of the lesion. The fibrous elements cast a radiolucent, cyst-like shadow. With the presence of osseous elements the opacity is increased and a ground-glass texture is assumed. Spotty areas of calcification may occur.

The craniofacial bones are a common site of fibrous dysplasia. There are reported here 4 cases involving the mandible, illustrating the varied clinical manifestations. Although the tumors are benign and are usually slow growing and self-limiting, there is great individual variability in the growth pattern. Young adults are usually affected.

There is no universal opinion as to management of fibrous dysplasia affecting the mandible. Most surgeons prefer the conservative approach. Surgery is reserved until facial disfigurement is noticeable, at which time a trimming operation for its cosmetic effect is performed. This procedure leaves the bulk of pathologic tissue intact. If the conservative approach proves ineffective (a small proportion of cases), radical resection is considered. Other surgeons advocate a more radical approach from the onset, since complete resection practically insures a cure.

The author suggests that the mode of therapy, whether it be watchful waiting, conservative surgery, or radical resection, will be dependent on the clinical behavior of the individual tumor.

Thirteen roentgenograms; 11 photographs; 5 photomicrographs.

STEPHEN N. WIENER, M.D.
Mt. Sinai Hospital, Cleveland

The X-Ray Findings in Instances of Missed Diagnoses in the Region of the Salivary Glands. K. Pfeiffer. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 819–828, December 1955. (In German) (Röntgeninstitut der Karl-Marx-Universität, Leipzig, Germany)

Upon reviewing a series of 250 consecutive cases of tumor-like swelling in the region of the parotid and submandibular glands, the author found 33 instances in which the clinical diagnosis was obviously wrong. In 17 of these the original impression was subsequently corrected by sialography.

In 10 cases a salivary gland ailment was diagnosed when the actual disease process was not in the gland but regional to it. Included in this number were such conditions as actinomycosis, chronic cervical adenitis, cervical tuberculosis, and metastatic cancer. In 8 instances tuberculous adenitis of the neck was diagnosed, when the actual disease was a salivary gland

tumor. In 8 cases, also, salivary gland calculi were falsely diagnosed. Three of these cases proved to be phleboliths in an angioma and two calcified lymph nodes. In only 5 among the entire 250 cases, was a salivary calculus missed.

Seven roentgenograms; 1 photograph; 2 diagrammatic drawings; 3 tables.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

THE CHEST

Lobar and Segmental Angiopneumography in Pulmonary Disease. Raúl Cicero and Hermilo Del Castillo. Acta radiol. **45:** 42–50, January 1956. (Department of Chest Diseases, Pab. 27, General Hospital, Mexico, D. F., Mexico)

Angiopneumography, as its name indicates, is a study of the pulmonary vessels. The contrast material (70 per cent Diodrast) may be introduced into the right heart through a catheter, with filling of the entire pulmonary arterial tree ("global" angiopneumography) or a catheter may be placed in an arterial branch of the lobe or segment to be studied, with opacification of only that section (selective angiopneumography). Higher injection pressures can, of course, be used in the latter approach.

The authors compared the two procedures in the same individuals. Their series included 146 examinations in 137 patients. In bronchiectasis, tuberculous fibrothorax, and after pulmonary resection some arterial branches not outlined by the global technic were visible with the selective procedure. Increased proliferation of the muscle layers in the first two conditions was thought to increase vascular resistance, with resultant decrease of the blood flow, which was reflected in poor visualization by global angiopneumography. This defect was overcome by the higher pressure of injection possible with selective angiopneumography. The variation after pulmonary resection was also explained on the basis of vascular resistance, which was felt to be secondary to overdistention of the remaining lung.

The arterial arborization is affected by various factors present in the diseased lung parenchyma. In pulmonary infarction there may be total absence of arterial filling, as a result of a thrombus situated in the lumen of the artery and obstructing the circulation. In caseopneumonic tuberculosis with large cavities there is distortion of vessels and slowing of circulation. Arborization is absent, with only a few thin vessels about the cavities. In early and miliary tuberculosis the vascular appearance is normal with apparently no change in the circulation through the poorly ventilated region.

Fourteen roentgenograms.

J. A. GUNN, M.D
Grand Rapids, Mich.

Simultaneous Multiple Pulmonary Angiolaminagraphy. Casimiro Simonetti and Italo Gigante. Am. J. Roentgenol. **75:** 129–139, January 1956. (Surgical Clinic of the University of Rome, Italy)

The authors advocate the use of simultaneous multiple angiolaminagraphy in the detection of the nature of pathological changes in the lung. In this manner a more precise study can be made of the behavior of the vascular pattern in and around a pulmonary lesion.

After a preliminary sensitivity test, 40 to 60 c.c. of the opaque medium (70 per cent Ioduron) is injected under high pressure into a vein of the elbow or *via* a cardiac catheter. The oscillation of the laminagraph is 20 degrees and exposures are made three, five, or eight seconds after the end of the injection, following a preliminary arm-to-lung circulation test with ether.

Seven cases are reported and the conventional and simultaneous multiple angiograms are presented. From these cases the following conclusions are offered: 1. When an echinococcus cyst is infected, collapsed or detached, functional changes are revealed by arterial spasm which is not present in a benign, slowly expanding cyst. 2. Recent suppuration is distinguished from chronic suppuration by diminished vascularization in the latter. 3. There is an increase in the vascular network around bronchiectatic lesions, usually with arterial spasm. 4. The vessels are altered in malignant lung lesions, *i.e.*, numerous irregular fine vessels in vascular tumors and irregular markings peripheral to the growth.

Forty illustrations.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

Peculiarities in the Roentgen Findings and in the Symptomatology Following Lung Resection. H.-L. Kölling. Fortschr. a. d. Geb. d. Röntgenstrahlen **84:** 34–40, January 1956. (In German) (Röntgenabteilung der Chirurgischen Universitätsklinik, Jena, Germany)

The rapid development of thoracic surgery has brought new problems to the radiologist. Following resection of a lung or part of a lung, a pleural effusion develops, which must be removed, first by drainage and later by aspiration. If a lower lobe is resected, the effusion develops in the basal portion of the thoracic cavity, and the roentgen diagnosis is simple. If the upper lobe or the middle lobe has been removed, then the effusion rides upon the lower lobe, which usually expands, at first mainly along the posterior wall of the thorax, forcing the effusion anteriorly and upward. As the lung and the developing fibrotic tissue take up the space of the effusion, the latter is gradually pushed into the apex until it disappears. Lateral views of the thorax usually show the forward and upward displacement of the fluid level.

If one whole lung has been removed, the organization of the pleural effusion also usually progresses from below upward. It is gradually diminished by retraction of the thoracic wall, elevation of the diaphragm, displacement of the mediastinal organs toward the side of the operation, fibrosis, and sometimes herniation of the remaining lung.

After an extensive lung resection certain changes are often observed in the abdominal organs. The elevation of the left diaphragm following left-sided resection causes an upward displacement of the splenic flexure, frequently with accumulation of a huge gas bubble. After extensive right-sided resections, the right diaphragm may shrink and, if the liver does not follow the upward movement, an elevation and an interposition of the right half of the colon are produced.

Unusual phenomena were also observed in the stomach after extensive resection of the right lung. In these cases the left diaphragm shows a marked increase in its respiratory excursions, producing intra-abdominal pressure changes. On expiration, the high elevation of the left diaphragm sucks the content of the stomach into the fundus; in inspiration the liquid content is pushed down into the antrum again. These pendulous

movements within the stomach may lead to rather severe disturbances in peristalsis.

Eleven roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Lymphoma of the Lung and Pleura. Willard Van Hazel and Robert J. Jensik. J. Thoracic Surg. **31**: 19–42, January 1956. (University of Illinois College of Medicine, Chicago, Ill.)

Twelve cases of lymphomatous involvement of the lung parenchyma or of the pleura are here reported. Most of these proved to be lymphocytic-type lymphosarcoma.

The radiographic appearance was extremely variable:

Case 1: A gradually increasing density in the left lung field which came to occupy two-thirds of the left chest.

Case 2: A dense, fairly well demarcated mass in the right lower lobe at the cardiophrenic angle.

Case 3: A solitary density in the left upper lobe just lateral and superior to the hilus. It was not sharply circumscribed, having an irregular border which merged into the adjacent lung tissue.

Case 4: A density in the right upper lobe which was considered to be an infarction or atypical pneumonitis.

Case 5: A density occupying the upper part of the right lung, with gradual opacification of the entire right lung field. Later a cavity and fluid level appeared in the region of the right upper lobe.

Case 6: Finely mottled, soft densities scattered through the right lung field, later enlarging and coalescing. These disappeared under x-ray and nitrogen mustard therapy.

Case 7: A large rounded mass in the region of the left lower lobe.

Case 8: A fusiform density at the right lateral chest wall and a soft, nodular, ill-defined density opposite the left pulmonary hilus. Other lesions later developed on the right, with formation of pleural fluid.

Case 9: Fluid in the left pleural cavity.

Case 10: Fluid in the left chest.

Case 11: Fluid in the right chest.

Case 12: Obliteration of the lung markings by fluid.

In summary: a circumscribed density was present in 4 patients; 1 patient with pleural fluid had 2 densities which were extrapleural and a density also in the opposite lung; 2 patients had massive pulmonary involvement; 1 patient had disseminated nodular disease. All the patients with pleural fluid exhibited typical fluid shadows.

Complete resection of the disease process was possible in 5 of the patients. Radiation therapy was used only in the pleural fluid cases, and then apparently not aggressively, so that its value was not impressive.

Twenty roentgenograms; 6 photomicrographs; 2 photographs; 3 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Primary Lymphoma of the Lung. Jack C. Cooley, John R. McDonald, and O. Theron Clagett. Ann. Surg. **143**: 18–28, January 1956. (Mayo Clinic, Rochester, Minn.)

There were found in the files of the Mayo Clinic 9 cases of lymphoma of the lung [over how long a period of time is not stated, nor is the number of cases of carcinoma of the lung seen at the same time given]. The series included 4 lymphosarcomas, 4 cases of Hodgkin's disease, and 1 reticulum-cell sarcoma. Eight of the cases were diagnosed postoperatively as bronchogenic cancer. Roentgen examination is of first importance, however, in indicating the presence of the neoplastic process.

Radiation therapy was used postoperatively [no details] with good results. Five of the 9 patients are still living at various intervals from two to over five years after exploration. One death occurred from surgical complications in the postoperative period, and 2 patients died suddenly of unknown causes after surviving several months.

Two photographs; 3 photomicrographs.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Thymus, Atelectasis, or Mediastinal Pleural Effusion? C. Esser and F. Hilgert. Fortschr. a. d. Geb. d. Röntgenstrahlen **84**: 3–18, January 1956. (In German) (Langenbeckstrasse 1, Mainz, Germany)

The authors discuss the probable factors that may produce the triangular or sail-like shadow often seen on the chest films of infants and discuss the three causes commonly mentioned in the literature, *i.e.*, paramediastinal pleural effusion, upper lobe atelectasis, and enlarged thymus. A paramediastinal effusion they believe is extremely rare. As to atelectasis, they sharply challenge and repudiate the views of Schmid (see following abstract). In their opinion an atelectasis of the upper lobe does occasionally occur in infants, but is always confined to the anterior portion of the lobe; its shadow on the x-ray film gradually fades away laterally and never causes the sharp outline seen in thymus enlargement. A well defined triangular shadow almost invariably represents the thymus. In this view, the authors are in agreement with Kemp, Morley, and Emrys-Roberts (Brit. J. Radiol. **21**: 618, 1948), from whose paper they quote freely. These latter writers obtained serial films of 700 healthy infants and found the typical triangular shadow in 44 cases, 31 times on the right side, 12 times on the left, and once on both sides. Two children came to autopsy and in each instance the shadow proved to represent the thymus.

Twenty-two roentgenograms; 3 drawings.

WILLIAM A. MARSHALL, M. D.
Chicago, Ill.

Thymic Hyperplasia or Upper Lobe Atelectasis? P. Ch. Schmid. Fortschr. a. d. Geb. d. Röntgenstrahlen **84**: 20–28, January 1956. (In German) (Kinderheilstatte Wangen im Allgäu, Germany)

There are great differences in the development of an upper lobe atelectasis in the adult and the infant. In adults the development is usually slow and gradual; in childhood the onset often occurs with dramatic suddenness, since the bronchus at this age is soft and the lymph nodes, which are chiefly responsible for the compression, react rapidly to inflammatory processes and become markedly enlarged. In children it is almost always the right upper lobe that is involved because the right upper lobe bronchus is much smaller than the left and because the larger part of the lymphatic apparatus, including the paratracheal node, is on the right side. In an adult the space of the collapsed upper lobe is taken up by both the lower lobe and the middle lobe. In the infant, only the lower lobe creeps upward behind the

middle lobe to fill the space created by the collapse of the upper lobe. The middle lobe itself retains its normal shape, and its horizontal upper fissure, which is located at the level of the mid-portion of the hilus, is well preserved, forming a roentgenologically distinct base line for the atelectatic upper lobe.

This is of great importance for the differential diagnosis between atelectasis and thymic hyperplasia. The thymus has no relation to the interlobar fissure of the middle lobe. Also, upper lobe atelectasis is almost always unilateral, while thymus enlargement is usually bilateral. Another differential feature is the characteristic convex lateral outline of the thymus. Of particular importance in making a distinction between atelectasis and an enlarged thymus is the lateral view. Here the straight lower border of the collapsed upper lobe can be seen at the level of the fissure (mid-portion of the hilus), while the lower border of a thymus is seldom distinct and usually not at this level.

Fourteen roentgenograms; 3 schematic drawings.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Joint-Like Cleft Formation in Calcified Cartilages of the Ribs in the Adrenogenital Syndrome. E. Fischer and H. Nowakowski. Fortschr. a. d. Geb. d. Röntgenstrahlen **84:** 57–61, January 1956. (In German) (E. F., Med. Univ.-Klinik, Kiel, Germany)

During the act of inspiration the anterior portions of the ribs undergo a certain degree of lateral movement and of torsion. This leads to a twisting movement in the joint between the costal cartilage and sternum, and to some bending and twisting in the cartilage itself.

The cartilage of the first rib usually becomes calcified quite early in life and its calcification, as a rule, is quite intensive. To overcome the consequent resistance to motion and to facilitate breathing, transverse gaps and pseudo-joints often develop across the cartilage. Along the edges of these gaps calcific projections (similar to osteoarthritic projections of bone) develop, which are an indication that movement takes place there. This is a normal process in the first rib. Ordinarily the cartilages of the other ribs become calcified only in advancing age, when respiratory movement of the bony thorax has become so diminished that pseudo-joint formation is no longer necessary.

If, however, most or all of the cartilages in a young person become prematurely calcified while vigorous thoracic breathing is still carried out, such secondary joints, gaps, and clefts may develop, more especially between the fourth and seventh ribs, where the greatest amount of motion takes place. These are most frequently found in association with the congenital adrenogenital syndrome which is characterized by premature ossification of the skeleton. The authors present such a case in which calcification of all the costal cartilages had taken place before the age of twenty. Typical pseudo-joints and clefts with marginal bone projections were demonstrable in the fifth to the seventh rib.

If in routine chest radiography attention is paid to the costal cartilages, one may occasionally find a slight transverse partial infraction of the cartilage with marginal calcific projections, formed on the same basis, to facilitate bending of the cartilage.

Two roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

THE CARDIOVASCULAR SYSTEM

Horizontal Body-Section Radiography as an Aid in the Diagnosis of Diseases of the Heart. G. Ch. F. Brinkbok. J. belge de radiol. **39:** 22–39, 1956. (In English) (Diaconessenhuis Hospital, Arnhem, Netherlands)

Cardiac fluoroscopy, routine postero-anterior, oblique, and lateral plain films, cardiac catheterization, and angiocardiography are established methods of studying cardiac disease. Ordinary body-section roentgenography has proved of little added value in the diagnosis of malformations of the heart. Horizontal or transverse tomography, however, reveals much about the anatomic relations of the different parts and it is possible that the value of this procedure may be enhanced by the production of pneumomediastinum.

The anatomic relations at various levels must be carefully considered. The section through the fifth thoracic vertebra passes through the aortic arch, which is to the left of the trachea. At the level of the sixth thoracic vertebra the ascending aorta forms the outer edge of the right side of the ventral part of the dense cardiac shadow, in front of the brachiocephalic veins. The large pulmonary arteries are behind the real cardiac silhouette and are best seen on the left side.

At a somewhat lower level, through the seventh thoracic vertebra, the anterior edge at the right side represents the right atrium. The greater part of the left side and posterior part are occupied by the pulmonary cone and the main pumonary branches.

At the level between the seventh and eighth thoracic vertebrae the posterior part of the cardiac shadow is produced by the left atrium. The superior vena cava is seen dorsally to the right.

The section through the eighth vertebra shows a round configuration. The right atrium is on the right, and the right ventricle is anterior. The left margin is the left ventricle. Only exceptionally is there a notch between the ventricles.

Transverse tomograms are reproduced to illustrate dextroposition of the descending aorta and enlargement of the right atrium in the tetralogy of Fallot; ventricular enlargement; aneurysmal dilatation of the primary pulmonary arterial segment; enlarged pulmonary arteries; enlargement of the left atrium in mitral stenosis.

Eleven roentgenograms; 8 drawings.

CHARLES M. NICE, JR., M.D.
University of Minnesota

The Effect of Posture and Respiration on the Slit Kymogram of Normals and Subjects with Mitral Stenosis. J. Leonard Brandt and Herman D. Ruskin. Am. J. Roentgenol. **75:** 160–164, January 1956. (J. L. B., 451 Clarkson Ave., Brooklyn 3, N. Y.)

Standardized slit kymography, as it records the diastolic filling of the left ventricle, provides useful data on the severity and type of many forms of heart disease. Direct translation of the movement of the left heart border as demonstrated kymographically into a curve on ruled paper after simple measurement provides comparable records under carefully standardized filming technics. This procedure is especially useful in evaluating mitral stenosis both before and after surgery.

Controlled study of 7 normal and 8 "mitral" subjects in erect and supine positions during five respiratory maneuvers revealed a marked difference in time and

amplitude of left ventricular excursion under different conditions in the same patient, in many instances. In the erect position, the apical portion of the ventricle fills rapidly in early diastole, the convexity toward the base tending to remain motionless or moving slowly leftward as the more basal portion elongates. Later the apex ceases to move as the basal portion fills. Thus more rapid leftward motion will occur in the upper portions of the left ventricle toward the end of rapid ventricular filling. Partly because of this effect and partly because of reduction in venous return in expiration, the erect posture minimizes the change in border motion seen in mitral stenosis. With the patient recumbent, in mid-respiration, elongation of the left ventricle is less marked and motion of both the apex and base of the ventricle is more uniform.

Five figures; 2 tables. DALE W. UNDEM, M.D.
University of Louisville

Radiological Kinetics and Pulmonary Arterial Pressure in Congenital Heart Disease. E. Donzelot, V. Serafini, J. Bougnoux, P. Kervoelen, and R. Heim de Balsac. Brit. Heart J. **18:** 35–43, January 1956. (Hôpital Broussais-la-Charité, Paris, France)

This paper, apparently the first work published on electrokymography of the pulmonary artery, should be read in the original by anyone interested in this procedure. The authors compared electrokymographic tracings with pressure curves obtained at catheterization. For normal hearts and in congenital cardiac lesions with increased flow in the pulmonary artery, the shapes of the curves were nearly identical. In conditions with decreased flow it was found possible to distinguish between valvular and infundibular pulmonary stenosis but a distinction was not always possible between infundibular and double (valvular and infundibular) stenosis.

Characteristic curves were obtained for Eisenmenger's complex, differing from those for other conditions with increased flow.

Nine sets of multiple graphs.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Diagnosis of Congenital Aortic Septal Defects. Description of Two Cases and Special Emphasis on a New Method which Allows an Accurate Diagnosis by Means of Cardiac Catheterization. H. A. H. D'heer and C. L. C. van Nieuwenhuizen. Circulation **13:** 58–62, January 1956. (Department for Cardiac Surgery, St. Anthonius Ziekenhuis, Utrecht, Netherlands)

A method of diagnosing aortic septal defect by the position of the catheter during cardiac catheterization is described. From the pulmonary artery the catheter can be pushed across the defect and into the ascending aorta, either downward toward the aortic valve or upward toward the arch and into a brachiocephalic artery. By superimposition of films taken with the catheter in each of these positions, the site of the aortic septal defect at some point beyond the origin of the two great vessels can be defined.

Conditions to be differentiated from aortic septal defect include patent ductus arteriosus, high ventricular septal defect, and truncus arteriosus. In the first of these conditions the catheter passes from the pulmonary artery into the descending aorta. In the presence of a high ventricular septal defect the catheter may pass into the "overriding aorta" and this situation may be difficult to distinguish from aortic septal defect. However, in aortic septal defect the catheter may often be withdrawn from an area of aortic pressure into one of lower pulmonary pressure. In some cases aortic and pulmonary pressures may be equal. In such a case the diagnosis of aortic septal defect may be indicated by withdrawing the catheter from the aorta into the region of the undivided pulmonary artery and then pushing it forward into a peripheral pulmonary artery, without encountering an area with a ventricular pressure pattern. This, of course, cannot be accomplished in the case of ventricular septal defect. Aortic septal defect can be completely differentiated from truncus arteriosus only by making the catheter take two directions after entering the aorta, as described above.

Thirteen illustrations, including 5 roentgenograms.

RICHARD G. LESTER, M.D.
University of Minnesota

Clinical Studies on Involvement of the Pulmonary Artery by Syphilitic Aortic Aneurysms. John J. Donnell, David C. Levinson, and George C. Griffith. Circulation, **13:** 75–81, January 1956. (University of Southern California School of Medicine, Los Angeles, Calif.)

Two cases of syphilitic aortic aneurysm compromising the pulmonary circulation are presented. In the first case an aneurysm of the ascending aorta and arch compressed the right pulmonary artery, causing an "acquired stenosis" with pulmonary hypertension proximal to the area of compression and a decrease in pressure beyond. In the second case there was a fistula between an aneurysm involving the entire arch of the aorta and the main pulmonary artery.

Clinically, the possibility that an aortic aneurysm is causing compression of the pulmonary artery system is suggested by evidence of right ventricular hypertrophy on the electrocardiogram. A fistula between an aneurysm and a pulmonary artery is suggested by a continuous murmur of the type heard with patent ductus arteriosus.

Diagnosis is confirmed by cardiac catheterization and angiocardiography. In the first case catheter study revealed a pressure of 50/12 in the main pulmonary artery as contrasted with a pressure of 15/8 in the right pulmonary artery distal to the compression. The angiocardiogram showed sequential filling of the right atrium and ventricle, the main pulmonary artery, and the left pulmonary artery. The right pulmonary artery, however, did not opacify. In the patient with the fistula, catheter study demonstrated the presence of a left to right shunt at the pulmonary artery level. Oxygen saturation in the right ventricle was 49 per cent and in the main pulmonary artery 77 per cent. The angiocardiogram revealed compression of the left pulmonary artery with absence of opacification of the left pulmonary circulation, but did not demonstrate the fistula. In each case late films showed opacification of the aneurysm.

Seven roentgenograms; 1 graph; 2 tables.

RICHARD G. LESTER, M.D.
University of Minnesota

Aneurysm of the Aortic Sinuses with Pseudo-Coarctation of the Aorta. Israel Steinberg. Brit. Heart J. **18:** 85–89, January 1956. (New York Hospital-Cornell Medical Center, New York 21, N. Y.)

The unique combination of an unruptured aortic sinus aneurysm and pseudo-coarctation is illustrated by

this single case report. Plain films showed nothing of the sinus aneurysm but disclosed enlargement of the descending aorta and the left subclavian, without rib notching. On angiocardiography the aneurysm was seen as a filling defect in the right atrium on the first films and later filled with contrast medium. The aortic arch showed a typical coarctation deformity but there were no dilated collateral vessels. Pressure in the femoral artery was normal; hence the designation "pseudo-coarctation."

Seven roentgenograms; 4 schematic drawings.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Correlation of Angiography with Surgical Treatment of Vascular Diseases. Gerald H. Pratt. Arch. Surg. **72**: 118–121, January 1956. (New York University College of Medicine, New York, N. Y.)

The author discusses various lesions of the vascular system from a diagnostic and prognostic standpoint, their delineation by angiography, and the use of this procedure in the selection of treatment.

I. Arteriography: With occlusion of a large artery, it is important to know the extent and type of collateral circulation available, so that treatment may be properly planned. Three types are recognized:

(1) Hypervascularization: The hypervascularization type shows minute vessels which were either preformed or developed as a result of the occlusion. These vessels, while they may maintain vitality of the skin and other tissues, cannot supply enough blood for normal activity of the part. Thus, patients with collaterals of this type only can have no direct arterial replacement because there is no adequate distal artery available for grafting.

(2) Supplemental Branches: This type of collateral circulation is by way of dilated and secondary vessels, such as occur about the knee joint. These are capable of enlarging and sometimes can carry the circulating load necessary for restricted physical activity.

(3) Bridging Collaterals: If the occlusion of a major vessel occurs slowly, there may be only minor circulatory deficiency, some of the blood flow having been detoured from the major vessels to other collaterals of the supplementary type until these have become enlarged. Most of the patients with supplementary branches or bridging collaterals can expect to have a good result from grafting if there is a good circulatory channel behind the block.

II. Venography after Phlebitis: By means of venography of the leg and thigh, one can determine the exact point at which to resect an incompetent vein. Many incompetencies of the peroneal system on the lateral aspect of the leg, which cannot be diagnosed clinically, have been found by this means.

III. Venography after Subclavian or Axillary Venous Thrombosis: By means of venography of the axillary vein, one can determine the site of obstruction and the extent of collateral circulation. Three patients were referred to the author with a diagnosis of varicose veins of the upper extremities. In 2 of these patients, the varicosities had been injected with sclerosing solutions, and a third had had repeated resection of these veins, which obviously were collateral vessels and were necessary for the return of blood flow from the periphery of the arms. Venography obviates such errors.

IV. Portal and Splenic Portagrams: Portagrams can be obtained at the time of surgery by injecting one of the major tributaries of the portal system, or preoperatively by injection of the spleen. This will demonstrate intra- and extrahepatic blocks and may prevent a grave error in the selection of an incision site as well as the type of shunt indicated for the relief of portal hypertension or other definitive operations. If the proximal portal system is blocked, a portacaval shunt must fail. If a very large splenic vein is present, that could be used for a shunt. If neither a portal nor splenic vein is available, an esophagogastrectomy or esophageal vein ligation or plication may be the treatment of choice.

HOWARD L. STEINBACH, M.D.
University of California, S.F.

Percutaneous Selective Angiography of the Main Branches of the Aorta (Preliminary Report). Per Ödman. Acta radiol. **45**: 1–14, January 1956. (Roentgen Department I, Sodersjukhuset, Stockholm, Sweden)

The author presents a method of selective angiography of the various branches of the aorta, which he has used since 1954. A radiopaque polythene catheter is employed. By immersion in hot water, this may be moulded in such a way that it is suitable for whichever branch of the aorta it is desired to examine. On rapid cooling it resumes its original elasticity while it remains fixed in the desired curve. It does not soften at body temperature but retains its shape after introduction into the vascular system. The catheter is inserted percutaneously *via* the femoral artery and, under fluoroscopic control, is passed into the desired vessel. The contrast material is then injected either manually or by a pressure apparatus.

The author has done 20 angiographic examinations by this technic, including studies of the innominate, left subclavian, celiac and renal arteries. He believes that the deleterious effects due to large amounts of contrast medium may be reduced by this method. No mention is made of any complication as a result of the procedure.

Twenty roentgenograms; 1 diagram.

J. P. CHAMPION, M.D.
Grand Rapids, Mich.

Thoracic Aortography by Percutaneous Transcarotid Catheterization. David Sutton. J. Fac. Radiologists **7**: 172–183, January 1956. (Radiological Department, St. Mary's Hospital, London, England)

This paper describes a method of catheterization of the thoracic aorta percutaneously, which has produced promising results in the hands of the author.

The technic is that used by Seldinger for the femoral artery (Acta radiol. **39**: 368, 1953. Abst. in Radiology **62**: 466, 1954). The carotid artery is used for introduction of the catheter, which is passed into the aortic arch and into the ascending aorta. Precise siting of the catheter tip is of vital importance, the ideal position being midway down the ascending aorta. Control films following injection of 5 c.c. of 50 per cent Diodone are obtained in order to define accurately the position of the tip before the main investigation proceeds. Thirty to 40 c.c. of 70 per cent Diodone is injected manually at a speed of about 20 c.c. per second.

The chief complication to be guarded against is hematoma formation. One of the author's patients experienced a homonymous visual defect which was believed to be secondary to a small embolus, possibly resulting from the formation of a thrombus during the insertion of the catheter.

The indications for thoracic aortography include congenital anomalies of the great vessels and the aorta, such as coarctation of the aorta, patent ductus arteriosus, aberrant subclavian artery or vascular ring; also, such acquired lesions of the great vessels as aneurysm or thrombosis.

The method has been used successfully 13 times in 12 patients. Of these, 6 had coarctation of the aorta and 6 had aneurysms or suspected aneurysms of the thoracic aorta. The data concerning these cases, with accompanying illustrations, are presented.

Twenty-seven roentgenograms; 1 photograph.

THEODORE E. KEATS, M.D.
University of Missouri

Selective Angiography of the Abdominal Aorta with a Guided Catheter. Hans Tillander. Acta radiol. **45:** 21–26, January 1956. (Centrallasarettet, Västerås, Sweden)

The widespread use of angiography and the occurrence of unfortunate complications have stimulated investigators to develop means which permit its more selective employment. In 1951 the author published a preliminary report on the use of a catheter with a flexible point controlled by a magnetic field (Acta radiol. **35:** 62, 1951). This method has now been further refined and tested clinically.

The apparatus consists of an electromagnet placed under the examination table, which must be made of non-magnetic material. The magnet is mounted on a carriage which can be moved parallel to the long axis of the table and at right angles to it. An x-ray tube with the beam in the horizontal plane, movable upward and sideways, is placed at one side of the table and directed at right angles to it so that the patient may be irradiated from one side to the other. Details of the construction of the magnet and the catheter are given.

The patient is placed in the supine position with the extended left arm on an arm rest attached to the examination table. The radial artery is opened about 10.0 cm. below the elbow and the catheter is introduced into it by a special instrument. The passage of the catheter into the descending aorta is usually done without the use of a magnet. Once in the aorta, the catheter is directed by the magnet and its movement observed fluoroscopically.

The procedure has been used chiefly for studies of the celiac artery and its branches and the renal arteries. Catheterization of the common hepatic and splenic arteries is possible, provided, of course, they originate from the celiac trunk.

About 20 examinations have been done by the method described here, without complications. Seven renal angiograms were attempted and 6 were successfully completed. Of 13 examinations directed to the celiac trunk, 8 were successful; in 5 cases the catheter could not be directed into the pre-selected artery. With the catheter in the gastroduodenal artery, an angiogram of the pancreas was obtained.

The disadvantages of the method are the rather complicated equipment and the surgical procedure required to introduce the catheter. The presence of aberrant renal arteries may lead to filling defects, but these appearances are highly characteristic. The advantages are that only the organ to be investigated is subjected to trauma by the injected medium; small amounts of a weak contrast medium may be employed, making it safe to repeat the examination if necessary; examination of otherwise inaccessible organs is possible.

Four angiograms; 2 photographs.

H. C. JONES, M.D.
Grand Rapids, Mich.

Occlusion of a Renal Artery as a Cause of Hypertension. Eugene F. Poutasse. Circulation **13:** 37–48, January 1956. (Cleveland Clinic, Cleveland, Ohio)

Three cases of malignant hypertension associated with partial or complete unilateral obstruction of a renal artery are reported, and a fourth, from the literature (Fisher and Corcoran: Arch. Int. Med. **89:** 943, 1952) is presented in summary. This diagnosis may be suggested by a sudden onset of high blood pressure preceded by an episode of abdominal or flank pain in the absence of a family history of hypertension. Urography may show impairment or absence of renal function unilaterally, though in some cases only diminution of renal mass with normal function or even a wholly normal pelvicalyceal system may be encountered. The definitive diagnosis is made by abdominal aortography, which demonstrates complete or partial obstruction of the renal artery or a branch on the affected side. In each of the author's 3 patients nephrectomy was followed by a drop in blood pressure to normal levels within several months.

Occlusion of a renal artery may be due to extrinsic cause, such as aortic aneurysm, hematoma, adjacent tumor, or twisting of the renal pedicle. Intrinsic lesions include thrombosis, embolism, arteriosclerosis, syphilitic arteritis, and congenital stenosis of the aortic orifice of the artery. The author emphasizes that, while occlusion of a renal artery with infarction of the kidney may result in hypertension, infarction can occur without associated change in the blood pressure.

Only a portion of the kidney need be infarcted to result in this syndrome. In 2 of the cases reported, aberrant renal arteries supplied small portions of the affected kidney; in the third case, involvement was limited to the major arterial branch to the lower pole and the occlusion was only partial.

The condition described is felt to represent a close parallel to the experimentally induced Goldblatt phenomenon. The condition is rapidly progressive, and the changes of malignant nephrosclerosis that will eventually occur in the non-ischemic kidney will result in death from renal insufficiency. Early surgical correction (nephrectomy) is therefore advised. If a partial occlusion without evidence of loss of function or atrophy is encountered, thromboendarterectomy may be the procedure of choice.

Six roentgenograms; 2 photomicrographs; 1 photograph; 1 table.

RICHARD G. LESTER, M.D.
University of Minnesota

Percutaneous Catheterization of the Renal Artery. Paul Edholm and Sven Ivar Seldinger. Acta radiol. **45:** 15–20, January 1956. (Roentgen Diagnostic Department, Karolinska Sjukhuset, Stockholm, Sweden)

The chief advantage of catheterizing the renal artery for arteriography is that it permits one to introduce an amount of contrast medium sufficient for examination of one kidney while at the same time avoiding injection into the other. The authors used this procedure in 9 cases, with successful results in 8.

The technic employed was that previously described by Seldinger (Acta radiol. **39:** 368, 1953. Abst. in

Radiology **62**: 466, 1954). It involves percutaneous puncture of the femoral artery, following which a catheter, the tip of which has been bent, is introduced with the aid of a metal guide. Under fluoroscopic observation the guide and catheter are pushed up into the aorta to the level of the renal artery. The guide is then partially withdrawn, and the catheter is placed with its bent tip toward the kidney to be examined and is moved along the aortic wall. When the opening of the renal artery is reached, the catheter moves outside of the border of the aorta in a readily recognizable manner.

For the arteriograms, 1 to 10 c.c. of 35 per cent, 50 per cent, or 70 per cent Umbradil is injected manually as rapidly as possible. One cubic centimeter of the 70 per cent solution was found adequate for visualization. By keeping the tip of the catheter near the opening of the vessel, arterial spasm is avoided and the chance of entering one of the branches of the renal artery is reduced.

The possible presence of aberrant renal arteries arising directly from the aorta diminishes somewhat the value of selective renal angiography, since a pathologic process may occur in a part of the kidney not supplied by the artery injected, or the non-injected area may be misinterpreted as an avascular tumor.

While it is too early for definite evaluation of this procedure, it appears that it may be entirely adequate in selected cases where special care of the kidneys is necessary.

Twelve figures, including 9 roentgenograms.

J. A. GUNN, M.D.
Grand Rapids, Mich.

Portal Venography. Anatomic and Physiologic Considerations in Interpretation. Francis F. Ruzicka, Jr., Guenther A. Doehner, and Louis M. Rousselot. Am. J. Digest. Dis. **1**: 3–21, January 1956. (St. Vincent's Hospital, New York, N. Y.)

The portal venogram can give considerable information concerning the physiology and anatomy of the portal circulation. The existence or non-existence of vessels of the portal system, their position, size, and relationships can be established, and congenital malformations of the cavernous type may be demonstrated.

Thrombosis of the portal vein is most frequently incomplete and difficult to recognize. It may present a ground-glass appearance without definite defect or may cause an actual defect in the vein. The site of obstruction is often well defined by portal venography. The collateral circulation may also be demonstrated. This is of two types: the detour type and the bridging type. The most frequent collateral systems are (1) the coronary esophageal, (2) the transhepatic, and (3) that arising from the splenic vein.

Physiologic deductions may be made from the anatomic information. Since normally only vessels lying along a direct course to the liver from the site of injection are visualized, all other vessels seen are to be regarded as a collateral system carrying blood around a block.

The portal venogram thus affords evidence of portal obstruction and suggests the possibility of portal hypertension. It furthermore offers the opportunity of deliberate thought concerning the question of sacrifice or preservation of a particular collateral vein or vein system in surgical planning.

[This paper presents in a rather general manner material given in much fuller detail in numerous other papers by the same authors. See, for example, Radiology: **64**: 675, 1935, and **66**: 206, 1956; also Surgery **34**: 557, 1953. Abst. in Radiology **63**: 290, 1954.]

Nine roentgenograms; 10 drawings.

ALEXANDER MARGULIS, M.D.
University of Minnesota

The Pattern of Occlusion in Atheroma of the Lower Limb Arteries. The Correlation of Clinical and Arteriographic Findings. G. E. Mavor. Brit. J. Surg. **43**: 352–364, January 1956. (Aberdeen Royal Hospital, Aberdeen, Scotland)

The author has studied 149 cases of atheroma with secondary thrombosis affecting the arteries of the leg. In 124 of this number there was peripheral ischemia without gangrene; in 25 there was early gangrene affecting the periphery.

Arteriography confirmed previous anatomical studies, which have shown that atheroma occurs most frequently in the femoral artery in the area of the adductor magnus opening and just above the knee joint. At the former point particularly, the artery is subject to unusual stresses, and it is of interest that in the author's series this was the most common site of secondary thrombosis. The observations indicate that thrombosis usually starts here and propagates proximally, eventually to reach the origin of the profunda femoris. This latter vessel is itself rarely thrombosed. The popliteal artery was the site of thrombosis in only 16 of the author's cases. The initial site is just above the knee joint. Propagation may be proximal or, more commonly, distal to the bifurcation of the artery.

Claudication is the chief symptom of main vessel thrombosis. In 88 per cent of the author's cases in which this occurred (excluding those in which both the femoral and popliteal arteries were involved), the thrombosis was limited to a short segment, indicating amenability to surgical reconstruction in the absence of certain contraindications.

Occlusion of the small vessels is said not to be of great significance except when complicating large vessel thrombosis, in which event gangrene invariably results. Gangrene itself carries a varying prognosis. Most cases are associated with main vessel thrombosis, and preventive measures offer the only hope in the claudication stage.

The author recommends a by-pass type of graft as the procedure of choice in lower limb thrombosis, since none of the collateral vessels are disrupted with this technic.

Thirty-three roentgenograms; 4 photographs; 6 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Functional Venography as an Aid in the Study of Peripheral Venous Disorders. Thomas C. Moore. Arch. Surg. **72**: 122–135, January 1956. (Ball Memorial Hospital, Muncie, Ind.)

Peripheral venous disorders arise largely from the difficulties associated with the passage of venous blood from the dependent extremity toward the heart, against gravity. Muscle activity and tonus provide the principal force producing this flow. Its direction appears to be determined by the valves, the push of blood from the capillary bed, and the proximal emptying of blood from the venous reservoirs by passage through the right side of the heart and by the negative intra-

thoracic pressures produced by respiratory movements.

The purpose of this report is to describe the findings in 70 functional venographic investigations carried out both in normal control subjects and in patients with venous disorders of the lower extremities. Injection into the superficial system, either percutaneously or through a cut-down polyethylene catheter, was performed in a majority of the studies. Thirty cubic centimeters of 30 per cent Urokon was generally used, and the injection was accomplished with the table tilted to an angle of 60°.

In the control studies, the opaque material, injected through a catheter, the tip of which generally was near the middle portion of the leg, passed up the greater saphenous vein for varying distances. Communicating veins were visualized at different levels, and the bulk of the contrast agent was seen to pass into the deep venous system and up the popliteal-femoral trunk against gravity in quiet but weight-bearing dependency. Some of the medium regurgitated past several valve stations after reaching the deep system. The material cleared from the deep system with exercise.

In patients with varicose veins due to incompetence of the superficial venous system, the venographic findings varied with the level of injection and the degree of damage to the system. When percutaneous injection was made directly into a dilated and clinically incompetent varicose vein, total retrograde passage of the radiopaque material was observed. At times the retrograde flow of medium in quiet dependency was observed to be partially diverted into the deep system; on other occasions it appeared to be unimpeded in its distal passage, with failure of the deep system to opacify. Injection through a polyethylene tube inserted from the medial malleolus to the level of the lower calf often resulted in the accumulation of some medium in local varices at the level of the tip of the tube and retrograde flow of the remaining medium back toward the ankle. The force of injection was not sufficient to cause proximal flow of the material in the incompetent vein or to produce initial opacification of the deep system in quiet dependency.

In cases of superficial phlebitis or its sequelae, the capacity of the superficial system to carry venous blood and to clear with exercise appeared to be impaired.

The deep system failed to opacify, following injection into the superficial veins in the lower calf or higher, only in those patients with deep venous obstruction or when the injection was made into a completely incompetent superficial vein with total, unimpeded retrograde flow. In the presence of obstruction, venous return is effected through the greater saphenous system, which opacifies in the thigh as well as in the leg. Normal appearing valves may be visualized, and the veins tend to be straight rather than tortuous. These veins clear completely with exercise.

Sixty-six roentgenograms.

HOWARD L. STEINBACH, M.D.
University of California, S. F.

Aortography: A Standardized Technique for the Investigation of Obliterative Vascular Disease. Alan Glen. South African M. J. **30:** 85–88, Jan. 28, 1956. (Pretoria, Union of South Africa)

The author describes a method of lumbar aortography for the investigation of obliterative arterial disease affecting the lower extremities. It is based upon the technic of dos Santos, of Lisbon. Good visualization of the entire arterial tree from the level of the diaphragm to the digital vessels of the toes can be obtained. By standardizing the technic as described, useful information concerning the speed of circulation and the state of the collateral vessels becomes available.

One drawing.

Spinal Cord Lesions Produced by Aortography in Dogs. Antone K. Tarazi, George Margolis, and Keith S. Grimson. Arch. Surg. **72:** 38–47, January 1956. (Duke University School of Medicine, Durham, N. C.)

The few serious complications which have occurred with aortography are said to have been caused by injury of organs which receive their blood supply directly from the lower aorta. Several cases have been reported in which damage has been done to the spinal cord, mesenteric circulation, or kidneys.

The study reported here was designed deliberately to produce spinal cord injury in dogs and to observe the roentgenologic, anatomical and histopathologic alterations. Sodium acetrizoate and iodopyracet were selected as the contrast media because of their general clinical use and because reports indicated that these chemicals were least toxic. From 7 to 20 c.c. was injected at one of three sites: (1) a point in the abdominal aorta just below the origin of the renal arteries; (2) a point in the abdominal aorta a few centimeters above the origin of the superior mesenteric artery; (3) the midthoracic aorta. It was observed that injections made above the superior mesenteric artery or in the midthoracic aorta caused less injury to the spinal cord than those made just below the renal arteries. This may be related to the diversion of part of the contrast material into the renal and mesenteric arteries. Injections below the renal arteries sent a less diluted mixture through the blood stream toward the orifice of the largest radicular artery, which was usually located at L-4 or 5.

These observations suggest that aortography on man through a puncture site 2 or 3 cm. above the superior mesenteric and renal arteries would be associated with better dilution than injections made near their origin or lower.

Those animals in which damage was produced to the spinal cord lay in the supine position when the injections were made below the renal arteries and above the superior mesenteric artery, and on the right side when the injections were made in the midthoracic aorta. Damage did not occur in 6 animals injected in the prone position. This indicates that the supine position favors the passage of the opaque material through the spinal arteries into the spinal cord.

It was observed that 15 c.c. of 70 per cent iodopyracet injected below the renal arteries produced spinal cord injuries less frequently and of less severity than 15 c.c. of 70 per cent sodium acetrizoate, which may be due in part to the high iodine content of the latter medium.

Five illustrations, including 2 roentgenograms.

HOWARD L. STEINBACH, M.D.
University of California, S. F.

THE DIGESTIVE SYSTEM

Method and Technic of the Radiographic Examination of the Esophagus and Cardia. H. Vernár and E. Veselá. Českoslov. Roentgenol. **9:** 4–16, March 1955. (In Czechoslovakian)

Roentgen examination of the esophagus and the

cardia must take into consideration the differences in the anatomy, functional characteristics, and innervation of these structures as compared with the remainder of the gastrointestinal tract. These peculiarities are often disregarded in the medical literature. Further difficulties arise from confusion in terminology, especially with regard to the cardia. Generally this is taken to mean the entrance of the esophagus into the stomach; anatomically, however, it is located in the gastric wall and forms the border between the stratified squamous-cell epithelium of the esophagus and the cylinder-cell epithelium of the stomach. The cardia is not identical with the so-called pars cardiaca, which is really the pericardial part of the stomach. Forssell speaks of a "constrictor of the cardia," and Rapant describes as the "subcardiac region" that part of the stomach which has as its lower limit a line drawn horizontally 2 cm. below the cardia. Schinz distinguishes between the superior and inferior cardia. In addition to innervation through the plexus of Auerbach and Meissner, a special motor mechanism is to be considered.

X-ray examination includes fluoroscopy and serialography (with special apparatus to depict the motor phenomena, if possible aided by contrast grid). Tracheoscopy was not available to the authors. Beside the ordinary barium meal, 40 per cent Opajol or Lipiodol was used as a contrast medium for demonstrating congenital abnormalities. Double-contrast and mucosal relief fillings were also employed. Modifications of the technic are indicated in affections of the hypopharynx and for such lesions as diverticula, ulcers, diaphragmatic relaxation and hiatal hernias, stenosis of the lumen, and tumors.

Twenty-four roentgenograms; 4 photomicrographs.

ERNST A. SCHMIDT, M.D.
Hilo, Hawaii

Examination Technic in Esophageal Varices. Marie Suntychová. Československ. Roentgenol. **9**: 17–19, March 1955. (In Czechoslovakian)

The author stresses the importance of repeated examinations, with different views under varying conditions (inspiration, expiration, Valsalva experiment, etc.), for diagnosis of esophageal varices. Results, with special regard to the changes in the mucosal relief, are described in 5 patients, of fifteen to fifty-eight years. With one exception, the clinical symptoms included repeated hematemesis. In one case cirrhosis of the liver was present, diagnosed by lienoportography and confirmed at autopsy. In the differential diagnosis, air bubbles, inflammatory mucosal changes, effects following acid or lye burns, carcinoma, and benign tumors must be excluded.

Fifteen roentgenograms. ERNST A. SCHMIDT, M.D.
Hilo, Hawaii

Lower Esophageal Web. Walter F. Bugden and J. Ernest Delmonico, Jr. J. Thoracic Surgery **31**: 1–15, January 1956. (State University of New York, College of Medicine, Syracuse, N. Y.)

Failure to demonstrate an esophageal lesion radiographically or by esophagoscopy often leads to an erroneous conclusion that dysphagia is functional. The complaint in several such instances has been shown to be due to the presence of a web-like ring projecting into the lumen of the lower esophagus. The limit to which these shelf-like processes dilate determines their relative obstructive potential. They may go unrecognized for long periods of time, and usually are not demonstrated unless carefully sought.

Roentgenograms show the web-like structures only when the esophagus above and below is distended with thick barium. Then a smooth, shelf-like, symmetrical shadow is seen. This is 3 to 5 mm. thick and constant in location. Above the area of narrowing produced by the web the lumen is not widened, and peristalsis is normal. There is little or no delay in emptying.

Stricture may be differentiated by the relatively longer and thicker area of involvement; also, stricture seldom shows the symmetry seen with esophageal web. These same points of differentiation will help to rule out cancer.

Pathologically the web is made up of hyperplastic squamous-cell epithelium, submucosa, and muscularis. Why it does not produce symptoms until late in life has not been explained. At esophagoscopy the narrowing may be misinterpreted as a tight cardiac sphincter unless the condition is kept in mind.

Treatment is surgical. Efforts at mechanical dilatation are generally unsuccessful.

Two illustrative case reports are presented and discussants of the paper mention 13 others.

Fourteen figures, including 11 roentgenograms.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

The Use of the Hyperventilation Effect in the X-Ray Diagnosis of the Stomach and Duodenum. Slavoj Věšín. Československ. Roentgenol. **9**: 29–31, March 1955. (In Czechoslovakian)

The author describes his method of combating spastic delay of peristalsis and gastric evacuation during x-ray examination by the use of simple hyperventilation. Discarding antispasmodics, he succeeds in obtaining lively gastrointestinal peristalsis, normal passage of barium through the pylorus, and good duodenal bulb filling within one or more minutes by deep inspiration. Essentially, the effect may be compared to that of morphine and its derivatives. Several case histories and illustrations demonstrate the value of this simple and clinically harmless method.

Five roentgenograms. ERNST A. SCHMIDT, M.D.
Hilo, Hawaii

Congenital and Acquired Syphilis of the Stomach, with Special Reference to the Gastric Deformity in the Various Stages, and a Report of Two Cases. Karl Mendl, Ritchie T. Jenkins, and J. Russell Hughes. Brit. J. Radiol. **29**: 48–55, January 1956. (Morriston Hospital, Swansea, England)

The evolutionary history of syphilis of the stomach cannot be followed radiographically until tertiary lesions have developed. Even then, the x-ray findings are not specific.

The earliest abnormal roentgenographic finding is a local area of induration which is caused by an infiltrative plaque. The infiltrate is mainly submucosal and may become fibrotic. This may overgrow locally to produce a filling defect, and ulceration sometimes occurs. Occasionally the infiltrate expands laterally instead of remaining localized. If in the antrum, such an occurrence produces a funnel-like stiffening which spares the pylorus; if in the pars media, an hour-glass narrowing may develop. When untreated, the process may

spread to involve any portion or all of the stomach. If the muscularis becomes involved, peristalsis ceases, and the linitis plastica or leather-bottle stomach is seen. The cardiac portion of the stomach is usually least affected, and the pylorus is nearly always widely patent.

The Wassermann reaction is almost invariably positive, and achlorhydria is present in advanced cases.

Of the 2 cases here reported, one was apparently acquired and the other congenital. The latter form is very rarely reported, but the radiographic findings are the same as in acquired syphilis, and differentiation must be made on other grounds.

Nine roentgenograms; 5 photomicrographs; 1 table.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

The Significance of Pharmacoradiology in the Differential Diagnosis of Prepyloric Ulcer. B. Gimes. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 771–775, December 1955. (In German) (Röntgenklinik der Medizinischen Universität, Budapest, Hungary)

Following initial fluoroscopy of the antrum and the duodenal cap, the author injects 0.005 gm. of morphine subcutaneously and resumes his study in five minutes. This tiny and obviously harmless dose causes the antrum to increase in size and to assume smooth contours. The pylorus opens widely. Any autoplastic irregularity of the rugae tends to disappear, and only true organic changes remain visible.

In some individuals, particularly those with a narrow S-shaped antrum, a cut-off that resembles an ulcer niche may be found on the lesser curvature aspect near the pylorus. The disappearance of such an imitation crater under the influence of morphine is illustrated. In a second case massive rugae plus prolapsing mucosa concealed an ulcer niche. Following morphine the rugae flattened out and the crater could be seen. One month later the ulcer became larger and could be demonstrated both with and without the drug.

Six roentgenograms. WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Malignant Gastric Ulceration. A Review of 26 Cases in Which There Was Delay in the Diagnosis. G. A. S. Lloyd and J. L. Morris. J. Fac. Radiologists **7:** 207–216, January 1956. (London Hospital, Whitechapel, London, England)

Malignant gastric ulcers early in their course present diagnostic problems. Either they may be missed entirely, or they may simulate benign ulcers. The authors studied 26 cases in which there was a delay of at least two months before a correct diagnosis was reached. Serial studies before laparotomy were available on most of these patients. The investigation covered the earliest changes in these neoplasms, their subsequent development, the applicability of classic criteria of malignant gastric ulceration to early lesions, and the major causes of delay in radiologic diagnosis. Ten illustrative cases are presented in summary.

Two main groups of neoplastic ulcers could be demonstrated. Those of the first group (15 cases) manifested themselves as flat, shallow, or saucer-like projections from the lesser curvature. The main problem here was one of recognition, as 9 of the lesions were not seen at the first examination. They may resemble a normal peristaltic wave or rugal fold. The second group (8 cases) showed a conical ulcer, with a crater much greater in depth than in transverse diameter. Here the difficulty was in interpretation. Six ulcers in this group were diagnosed as benign and presented all the criteria of benignity. The authors stress the point that converging mucosal folds into the base of the crater do not necessarily mean benign ulceration.

Ulceration of either type at or about the incisura angularis often produced a lesser curvature shortening recognized by failure to demonstrate a normal incisura. The authors feel that the incidence of this latter finding is significant enough to warrant suspicion of malignancy and to call for gastroscopy. In both groups, as the lesion progressed, it became an ulcer within a filling defect.

In 3 cases benign ulceration was found in association with, but discrete from, a malignant neoplastic ulcer of the stomach.

Fourteen roentgenograms.

STEPHEN N. WIENER, M.D.
Mt. Sinai Hospital, Cleveland

Benign Gastric Tumors (Diagnostic Difficulties). Umberto Ballarati. Radiol. med. (Milan) **42:** 31–43, January 1956. (In Italian) (Ospedale di Circolo di Busto Arsizio, Italy)

The 13 cases of benign gastric tumors covered by this report included 3 of *multiple diffuse tumor* (diffuse polyposis), 5 of *small isolated tumors* (4 solitary polyps; 1 circumscribed polyposis), and 5 of *large isolated tumors* (soft fibroma of the anterior wall, neurinoma of the lesser curvature, fibroadenomatous polyp of the antrum, another antral polyp, and recurrent polyp with malignant change). A correct preoperative diagnosis was achieved in 8 of the series. Twelve cases were histologically verified; the remaining case was observed gastroscopically and followed periodically.

The roentgen differentiation between benign and malignant gastric tumors is often so unrewarding that some authors will not go beyond the statement of "circumscribed tumor." Simonsen's triad (Röntgenpraxis **6:** 663, 1934. Abst. in Radiology **24:** 387, 1935) may be of help, *i.e.*, smoothly defined filling defect, surrounded by well preserved mucosal folds and mobilized by peristaltic waves.

Small isolated polyps, once detected, can be confused only with aberrant pancreatic tissue. The difficulties arise from the fact that certain benign tumors (usually of larger size) simulate cancer, while malignant tumors sometimes have benign features, particularly when located in the antrum. Finally, one must be very cautious when faced by a benign tumor which has shown notable growth, especially if it has an ulcerated surface, because of the possibility of malignant change.

Fourteen roentgenograms. E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

Enterogenous Cyst of the Stomach Wall, a Rare Benign Lesion. Case Report. Stephen B. Dewing, Carl W. Roessel, and Edwin V. Olmstead. Ann. Surg. **143:** 131–135, January 1956. (Hunterdon Medical Center, Flemington, N. J.)

Enterogenous cysts of the stomach are of rare occurrence. The authors believe the case recorded here to be the seventeenth in the literature. It was an incidental finding, high in the fundus, about 3 cm. in the diameter, non-ulcerated and non-obstructing. It was seen fluoroscopically and on the films as a smooth intraluminal filling defect. After surgical removal,

microscopic study showed it to be in the submucosal layer of the stomach wall. No evidence of malignancy was found.

Two roentgenograms; 2 photomicrographs; 1 photograph.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Remarks on the Problem of Gastric Mucosal Prolapse. L. Megay. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 761–770, December 1955. (In German) (Szövetség u. 14, Budapest, VII, Hungary)

There is not only a difference of opinion as to the clinical picture and treatment of transpyloric prolapse of the gastric mucosa, but also some question of its existence or non-existence. While Zimmer (1950) considers it a specific disease entity, Golden (1952) and Katsch (1953) regard it as a phase of antral gastritis. Baensch (1952) calls the findings normal and Pohlandt (1955) states that prolapse is a radiologic artefact. The author believes that the truth lies somewhere between these diverse views, for there now can be no doubt that the mucosa can prolapse.

The autoplastic character of the gastric mucosa, which depends upon the contraction of the muscularis mucosa and represents the local adaptation of the mucosa to gastric content, has been well described by Forssell. In the consideration of autoplasty it should be noted that the mucosa is loose and that its area is twice that of the muscularis. One should not be surprised that this redundant lining does evaginate through the pylorus into the duodenum. This does not differ from the evagination that occurs at the cardia of the stomach, at the ileocecal valve, at the anus, and at sites of intestinal anastomoses. Normal pyloric function could by no means stop this prolapse. Large food particles, foreign bodies, stalked and unstalked gastric polyps, all readily enter the duodenal cap. As a matter of fact, the mucosa behaves like an unstalked polyp.

In any one case all phases of prolapse may be seen, from pronounced evagination, through an intermediate state, to a condition with all the mucosa returned to the stomach. These phases may be present both in normal individuals and in those with disease. Whether there is any connection between prolapse and gastritis is still dubious. The only fact that has thus far been determined is that the phenomenon exists.

Sixteen roentgenograms; 1 photograph.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Radiologic Study of Duodenal Stenoses by Adhesions and Volvulus in Infants and Children. J. Lefebvre, J. Sauvegrain, D. Pellerin, G. Anguenot, and J. Bennet. J. de radiol. et d'électrol. **37:** 1–11, January-February 1956. (In French) (Service central d'Électroradiologie de l'Hôpital des Enfants malades, Paris, France)

Early in embryonic life the digestive tube is in the sagittal plane. At the eighth week the primitive intestinal loop elongates and undergoes a counter-clockwise rotation of 90° before leaving the abdomen by the umbilical orifice. At the end of the eleventh week the loops again enter the abdominal cavity, rotating a further 180° in the same direction, to attain the adult position. From this time until birth the posterior peritoneal attachment develops at the duodenojejunal juncture and the left and right colon are attached to the posterior abdominal wall.

Anomalies of embryologic evolution may occur. The intestinal loop may not rotate; in this case the second, third, and fourth portions of the duodenum descend in the right flank, and the jejunum occupies the hypochondrium and right flank (mesenterium commune); the colon is entirely on the left. With this arrangement there may be absence of the posterior attachments, predisposing to volvulus, or there may be abnormal attachments in the form of adhesive bands, which are particularly frequent in the duodenal region. Again, there may be correct rotation of the intestinal loop, but with anomalous peritoneal attachments. Defective attachment may result in volvulus of the right colon. Excessive or superfluous attachments lead to adhesive bands in the duodenal and cecal regions, exaggeration of the ligament of Treitz, or exaggeration of the cysticoduodeno-colic ligament. The bands may cause folding of the duodenum on itself: D1 on D3, D2 on D3 or on D4.

Among 45 patients with duodenal stenosis there were 18 with common mesentery, 26 with adhesive bands, 15 with a combination of bands and volvulus, and 4 with volvulus alone.

Radiologic examination affirms the duodenal stenosis and may give information concerning causative factors. Vomiting of bile-stained material usually indicates that the stenosis is distal to the ampulla of Vater.

Details of the 45 cases are tabulated.

Thirteen roentgenograms, with accompanying sketches.

CHARLES M. NICE, JR., M.D.
University of Minnesota

Intussusception: An Appraisal of Present Treatment. Thomas V. Santulli and Jose M. Ferrer, Jr. Ann. Surg. **143:** 8–17, January 1956. (College of Physicians and Surgeons, Columbia University, New York, N. Y.)

Radiology has come into its own! Here is an article written by surgeons, published in a surgical journal, but essentially recommending a radiological procedure over surgery.

The experience with intussusception (41 cases) over the past five years (1949–1954) at Babies Hospital (New York City) was reviewed. Thirty cases were treated by barium enema introduced under fluoroscopic control, and in 18 complete reduction was obtained. Criteria of success are complete filling of the cecum and ascending colon, with reflux into the terminal ileum, disappearance of the mass, subsidence of pain, passage of gas and feces with the barium, and improvement in the patient's general condition. If these criteria are not fulfilled, immediate operation is indicated.

Two deaths occurred in the series, both in severely ill children with diarrhea for several days before intussusception was diagnosed. One died during administration of the barium enema; the other after surgery, without having been examined roentgenologically.

Advantages of non-operative treatment are the absence of surgical and anesthetic complications and the shorter hospital stay. Of the disadvantages, the one most seriously to be considered is the drain on the vitality of a severely ill patient in whom the reduction by enema is incomplete. Other possible objections to the procedure are the danger of overlooking lesions which may be responsible for the intussusception; inability to demonstrate the enteric form of intussusception above the ileocecal valve; and finally the possibility of perforation or reduction of a gangrenous bowel. The method should never be used in patients showing

any evidence of peritoneal irritation, which may indicate a compromised circulation to the bowel, and probably is contraindicated in patients with a history of more than twenty-four hours.

The responsibility of the surgeon for the choice of treatment and its execution is stressed. He should always be at hand to operate if non-surgical reduction fails.

Eight roentgenograms; 1 photograph; 5 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

The Problem of Early Diagnosis in Right Colon Carcinoma. Robert P. Schutt and John H. Walker. West. J. Surg. **64:** 29–34, January 1956. (Mason Clinic and Virginia Mason Hospital, Seattle, Wash.)

The objective of increased survival rates among patients with carcinoma of the cecum, ascending colon, and hepatic flexure demands earlier diagnosis in this group. Because there is no clear-cut clinical pattern, there has been a significant lapse between the onset of symptomatic disease and diagnosis in many cases. In the group of 73 patients analyzed by the authors, the average duration of symptoms before diagnosis was 10.2 months. Fifty per cent of these patients had been seen by their physician one month or more before the proper diagnosis was established.

The most common initial complaint (in 40 per cent of the patients) was abdominal distress, variously described as cramping, bloating, or dull aching. Only one-fourth of the patients lateralized their pain to the right side. Alteration in bowel habit was the initial complaint of less than 25 per cent and was almost equally divided between constipation and diarrhea. Twenty per cent of the patients complained initially of weakness or fatigue. Usually this is due to a hypochromic anemia as a result of chronic blood loss. The fact that this anemia will respond to iron therapy has been the cause of many delays in diagnosis. By the time of admission to the hospital, 62 per cent of the patients had a significant degree of anemia. Other complaints, such as weight loss, gross blood in the stool, presence of a mass, anorexia, nausea, vomiting, and pallor, were observed less frequently.

Five per cent of the patients underwent appendectomy during the time that symptoms indicative of carcinoma were present. The authors believe that the possibility of cancer of the right colon should be considered in every adult patient with a diagnosis of acute or recurrent appendicitis.

Roentgen study is the most important part of the examination of the patient suspected of having a carcinoma of the right colon. Since a single examination of the colon may be negative in the presence of a carcinoma, the possibility of a missed lesion should always be considered and a report of normal should not be regarded as final by the clinician. An ideal roentgenographic examination may not be obtained for one or more of several reasons: feces in the cecum; desire of the patient to relieve himself before the study is completed, due to bowel distention; rigidity of the abdomen with resultant difficulty of palpation; superimposed loops of sigmoid colon or barium-filled small bowel, especially in the case of a low-lying cecum. Close cooperation between the radiologist and clinician is advised, and the value of repeated examinations in obscure cases is stressed.

In the series reported there was an overall five year survival rate of 37.5 per cent, and for the group undergoing resection for cure, 54.5 per cent.

Six roentgenograms; 3 tables.

RICHARD G. LESTER, M.D.
University of Minnesota

New Paths Opened by Biligrafin for the X-Ray Examination of the Biliary Tract. St. Lajos. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 776–784, December 1955. (In German) (II. Klinik für Innere Medizin der Medizinischen Universität Szeged, Hungary)

Biligrafin, now in use for two full years, has filled some of the gaps previously present in the investigation of the biliary tree. The absorption factor which must be taken into account with an orally administered agent is eliminated. One is strictly concerned with the concentration ability of the liver and with the function of the common duct with its sphincter. It is unfortunate that a hypertonic common duct and a hypotonic sphincter cause some reduction in the concentration of the medium as seen in the ducts. This phenomenon can, however, be reversed by administration of morphine, which by causing spasm is helpful in keeping the common duct filled.

When the gallbladder is present, there is no significant widening of the common duct under the influence of morphine. The gallbladder takes up any increase in pressure and dilates. In other words, it acts as a protector of the liver parenchyma. Since the gallbladder will take up the concentrated bile, quite frequently the common and cystic ducts themselves cannot be demonstrated. If one is still desirous of demonstrating the ducts in the presence of a gallbladder, a second dose of Biligrafin may prove useful.

The author's technic of studying the biliary tree with Biligrafin is to administer 20 c.c. of the medium intravenously, with the patient lying on the right side. In twenty minutes a film is taken. If the ducts are not visualized, an additional 20 c.c. plus 0.01 gm. of morphine is given.

It is pointed out that, in addition to gallstones, one should look for stenosis at the papilla, a stone in the common duct, pancreatic reflux, and functional enlargement of the common duct.

Ten roentgenograms.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Intravenous Cholangiography in the Post-Cholecystectomy Syndrome. Conway Don and Hugh Campbell. J. Fac. Radiologists **7:** 197–206, January 1956. (University College Hospital, London, England)

The radiologic investigation of patients with the so-called "post-cholecystectomy syndrome" has recently received impetus with the introduction of Biligrafin. In order to assess the significance of changes in the common duct, the authors compared intravenous cholangiograms of 39 asymptomatic post-cholecystectomy patients with those of 23 patients suffering from the "post-cholecystectomy syndrome."

Four patients with post-cholecystectomy pain were found to have stones in the common bile duct and 1 a stone in the cystic duct stump. None of the symptom-free patients showed stones, and these are therefore considered of definite significance in the syndrome under discussion. A persistent cystic duct stump (in 3 of the symptomatic group) and kinking and distortion of the ducts (in 1) were considered of possible significance.

Because it was such a frequent occurrence in symptom-free patients, dilatation of the bile-ducts was considered to be of no significance in a patient with symptoms after cholecystectomy; similarly, no significance could be attached to constriction of the ducts or to biliary stasis.

The authors' observations do not favor the view that dilatation of the ducts is a usual post-cholecystectomy occurrence or that it is an indication of biliary dyskinesia. Their studies indicate that such dilatation is a permanent result of back-pressure, owing to obstruction of the common duct by stones at an earlier stage.

Sixteen roentgenograms; 2 tables.

STEPHEN N. WIENER, M.D.
Mt. Sinai Hospital, Cleveland

Observations of the Bile Ducts after Cholecystectomy. F. Heuck and F. Leupold. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 784–792, December 1955. (In German) (Medizinischen Universitätsklinik Kiel, Germany)

Fifty-two patients with post-cholecystectomy complaints were examined following intravenous administration of Biligrafin. These patients fell into four groups: (1) those with common duct stones; (2) those with anatomic abnormalities of the common ducts; (3) those with normal ducts but with persistent symptoms; (4) those with ductal-enteric anastomoses.

Once the ducts were visualized, serial films were taken following the oral administration of egg powder. Failure of the common duct to contract was considered an indirect sign of inflammation.

Common ducts containing calculi were found to be dilated but these same ducts remained dilated after the removal of the stones. Thirty-two patients showed widening of the common duct, this number including patients both with and without stones, as well as some without symptoms. In addition, it was shown that the stones in the common duct could shift their position without producing any symptoms.

Narrowing of the common duct was ascribed to stricture formation in most instances, but was without symptoms. When the duct widened above a narrowed area, it was noted that the stump of the cystic duct and also the hepatic ducts dilated. This same observation was made in cases of angulation of the duct.

It was noted further that regeneration of the gallbladder from the stump of a cystic duct tended to occur in almost all instances if a suitable time interval were allowed. Diagnostic confusion could occur in terms of a retained gallbladder or an actual common duct diverticulum, but the very rarity of these latter conditions is to be borne in mind. In one instance retrograde filling of the duodenal cap was for a time considered to represent a regenerated gallbladder.

Functional disturbances of the sphincter of Oddi must occur, but the radiographic signs are doubtful.

Nine roentgenograms.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Delayed Filling of the Gallbladder through Retention of Contrast Material in the Stomach. A. Ravelli. Radiol. clin. **25:** 55–56, January 1956. (In German) (Röntgeninstitut der Chirurgischen Universitätsklinik, Innsbruck, Austria)

The author previously reported a case with retention of gallbladder contrast medium within the stomach and absence of gallbladder filling, as a result of a duodenal ulcer which was revealed by a gastrointestinal series a few moments later (Acta gastroenterol. belg. **17:** 154, 1954). The three-hour film showed the stomach emptied and a faint gallbladder shadow.

The case reported here is similar, with fourteen-hour retention of the medium in the stomach and with only faint visualization of the gallbladder. Four hours later the contrast material had left the stomach, and the gallbladder shadow was dense. In contrast to the first case, no abnormality was found in the gastrointestinal tract on subsequent examination.

It would seem that retention of the medium in the first instance was due to a reflex pylorospasm occasioned by the duodenal ulcer. In the second patient, it can be assumed that the contrast material in the stomach caused a chemically induced reflex which led to a persistent closure of the pylorus.

[For another extrabiliary cause of poor gallbladder filling by the oral method, see May and Moussard: J. de radiol. et d'électrol. **36:** 876, 1955. Abst. in Radiology **67:** 460, 1956.]

Two roentgenograms.

CHRISTIAN V. CIMMINO, M.D.
Fredericksburg, Va.

THE MUSCULOSKELETAL SYSTEM

Fluorosis in Nalgonda District, Hyderabad-Deccan. A. H. Siddiqui. Brit. M. J. **2:** 1408–1413, Dec. 10, 1955. (Osmania Medical College, Hyderabad-Deccan, India)

Thirty-two advanced cases of fluorosis, with neurological manifestations, were investigated. The degree of disability and the time of onset of symptoms in these cases were related to the concentration of fluorine in the water and the length of time of its ingestion. In the village in which the concentration of fluorine was the highest, symptoms of intoxication appeared in immigrants into the area within one to four years. The severity of the disease had a definite relationship to meteorological factors, *e.g.*, temperature, and to the economic and nutritional status of the population. Hot weather not only increases the water intake but also increases the concentration of fluorine and the ingestion of an abnormal amount of sediment. The degree of disability was also related to physical strain, being most pronounced in manual laborers. Children, apart from dental changes, do not suffer from the ill effects of fluorine, probably because the growing tissues are somehow able to deal with it. In the 7 patients in whom eighth-nerve functions (audiometry and caloric tests) were investigated, a marked loss in hearing for the higher frequencies was found, indicating a degenerative lesion which the author thinks may be due to pressure of new bone formation around the organ of Corti.

Roentgen studies demonstrated sclerosis of the bones throughout the skeleton. In the less advanced cases the cancellous bones showed accentuation of the trabecular structure due to thickening. Later the trabeculae coalesced and gave an increased density to the bone, which seemed to be granular or amorphous in structure. Where the sclerosis was complete, the bones appeared chalky and structureless. These progressive changes were best observed in the pelvis and spine. Sclerosis was noted in the body, the transverse

and spinous processes, and the pediculate articulations of the vertebrae. The margins of the transverse and spinous processes were irregular owing to new bone formation. The intervertebral ligament showed calcification. Lipping of the vertebral bodies, especially in the lumbar region, was common. In the thoracic region the costovertebral articulations added an extra density and irregularity to the lateral margins of the spine.

In the pelvis the sclerosis was more pronounced around the sacroiliac and hip joints. The capsule of the hip joint was calcified. The exostoses from the iliac spine were less marked. The crest of the ilium, the ischial tuberosity, and the margins of the sacrum invariably showed exostoses and, in advanced cases, the ligaments attached to them were ossified. There was lipping of the acetabulum, and exostoses were observed on the trochanters of the femur.

The cortical portions of the long bones were dense and thick, with a reduction of the marrow cavity due to endosteal bone formation. Periosteal bone formation was also noted and was best visualized in the areas of tendinous, fascial, and muscular attachments.

Sclerosis around the suture line was often observed in the vault of the skull. In advanced cases there was marked thickening in the vault and base. In 4 cases the air cells were narrowed and in 4 the clinoid processes were thick and dense. These changes have not been mentioned by others.

The fluoride level in the blood was persistently low in the present series. Urinary fluoride excretion varied between 1.2 and 5.8 p.p.m. A case is described in which excretion of previously stored fluoride continued in the urine at a high level ten years after the patient had left the endemic area.

Four roentgenograms; 3 photographs; 5 tables.

Osteochondrodystrophy as a Result of or in Relation to Pseudo-Hypoparathyroidism. George J. Garceau and Wallace E. Miller. J. Bone & Joint Surg. **38-A:** 131–141, January 1956. (James Whitcomb Riley Hospital, Indianapolis, Ind.)

Pseudo-hypoparathyroidism (sometimes known as the Seabright bantam syndrome) is a condition characterized by a failure of bodily response to normal parathyroid secretion. Parathyroid hormone normally cuts down the reabsorption of phosphate in the renal tubules, so that in this disorder the serum inorganic phosphorus becomes elevated. There is associated lowering of serum calcium, which is in part achieved by deposition of calcium in the soft tissues. Skeletal deformities reflecting early closure of epiphyses are seen as well. Occasionally, non-characteristic skeletal changes are observed, as in the case reported here.

The patient, a child, was in more or less chronic tetany. Laboratory findings seemed to confirm the impression of pseudo-hypoparathyroidism. Roentgenographic studies showed enlargement of the skull with widening of the diploic space and thickening of the outer table. Patchy areas of increased density were present over the calvarium. There appeared to be disorganization of the metaphyses at the epiphyseal lines, with flaring and premature closure of epiphyses. The ribs showed cystic changes. The spine was osteoporotic.

The findings were interpreted as representing advanced osteochondrodystrophy, quite like Morquio's disease. Deformities became gradually more exaggerated and grotesque during a five-year period of observation.

Serum calcium, phosphorus, and alkaline phosphatase were brought to normal levels by the administration of AT 10, vitamin D, and a high calcium diet. Progress of the deformities was controlled by corrective surgical and medical measures. Whether or not treatment will need to be changed as maturity is reached remains to be seen.

Fourteen roentgenograms; 9 photographs; 1 photomicrograph; 1 chart; 3 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Hemangiomatosis of the Skeleton and the Spleen. Gorton Ritchie and Francis G. Zeier. J. Bone & Joint Surg. **38-A:** 115–122, January 1956. (Milwaukee Children's Hospital, Milwaukee, Wisc.)

Bone hemangioma is most commonly found in the spine, and next most commonly in the skull. Multiple hemangiomata throughout the skeleton are rare, especially in association with involvement of the spleen. Attention is called to the latter entity by this report of a case.

Widespread lesions were present throughout the skeleton, excepting the epiphyses and the bones of the hands and feet. The spleen was enormously enlarged, containing multiple cystic nodules and large vascular spaces. Splenectomy led to a diagnosis of hemangiohamartoma.

Skeletal roentgenograms revealed numerous irregular, multilocular, and monolocular cystic lesions. In the skull these areas were as much as 1.5 cm. in diameter, and had a moth-eaten appearance. The frontal and parietal bones and mandibles were involved. The ribs and long bones showed oval lesions which were intramedullary, causing local expansion and cortical thinning. The patient, first seen at the age of two, now seven years old, has had four fractures through bony lesions from relatively slight trauma.

The authors point out that flat bones such as the scapula, pelvis, and skull may show a sunburst pattern of new bone radiating from a point on the surface. When vertebral bodies are involved, coarse, vertical trabecular striations are seen, sometimes extending into the vertebral arch. The tubular bones characteristically show multilocular, soap-bubble, cystic lesions with loculi somewhat smaller than those in giant-cell tumor and bone cyst. If the bone is expanded, the cortex is usually intact.

Cavernous hemangiomata are more common than the capillary type, and may expand gradually because of intravascular pressure. Occasionally the lesions undergo spontaneous regression and healing, and the vascular tissue may be replaced by bone.

Four roentgenograms; 2 photographs, 3 photomicrographs.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Ankylosing Spondylitis. J. H. Middlemiss. J. Fac. Radiologists **7:** 155–166, January 1956. (Radiodiagnostic Department, United Bristol Hospitals, Bristol, England)

The radiological appearances in ankylosing spondylitis are explained in terms of inflammation, reaction, and repair. Connective tissue is primarily involved, and the usual sites are the sacroiliac joints and the joints and ligaments of the spine, though other areas,

especially around the pelvic girdle, are not uncommonly affected. Peripheral joints and connective tissues may also be involved, as the hip joint, the greater trochanters of the femurs, and the connective-tissue attachments on the os calcis.

The initial change is bone destruction, apparent radiologically as osteoporosis. The course at any one point is self limiting, repair and healing taking place in a predictable pattern along connective-tissue planes.

Ankylosing spondylitis is seen predominantly in young men but may occur in older men and in women. In the latter a different pattern of disease is not uncommonly present. The predominant, though not invariable, female pattern is the "streaky" type. The common features are marked involvement of the posterior spinal articulations; little or no ligamentous ossification; osteoporosis; considerable calcification of costal cartilage. It is not clear what the significance of these features is. If, in fact, there is a difference between the sexes in the predominant radiological pattern, as the writer considers there is, it is suggested that it may be based on an endocrine factor.

Some of the similarities to rheumatoid arthritis and certain points of differentiation from that condition are discussed. In ankylosing spondylitis the peripheral joints may be involved, just as rheumatoid arthritis may cause involvement of the diarthrodial joints of the spine. Rheumatoid arthritis of the spine is often diagnosed as ankylosing spondylitis, and the peripheral joint involvement of ankylosing spondylitis is almost invariably attributed to rheumatoid arthritis. The author suggests that these two conditions have a different "pattern." There are few authenticated published cases of ankylosing spondylitis occurring before puberty and only rarely is it seen before the age of seventeen in contrast with rheumatoid arthritis. The differences between the two conditions are as follows:

	Ankylosing Spondylitis	Rheumatoid Arthritis
Involved early	Sacroiliac joints	Peripheral joints
Sacroiliac joints involved	Yes	No
Spine involved	Yes, ascending	Usually only cervical spine
Connective tissues around pelvic girdle	Frequently involved	No
Peripheral joints involved	Rarely	Yes
Periarticular or paraspinal ossification	Yes	No
Symphysis pubis involved	Yes	No
Bony ankylosis of joints	Yes	Uncommonly
Osteoporosis	Less commonly	Commonly

The detailed bone changes in any one joint are indistinguishable from those of rheumatoid arthritis. There is progressive destruction of articular cartilage, destruction of articular cortex, and destruction of subarticular bone. However, the overall pattern is different. The generalized osteoporosis often associated with rheumatoid arthritis is usually absent in peripheral joint involvement in ankylosing spondylitis. There is rarely ulnar deviation or varus deformity, since the muscle changes that occur in rheumatoid arthritis are not usually seen. The destruction of the articular cortex in ankylosing spondylitis appears much more at the joint margins and progresses away from the joint toward the shaft rather than toward the articular cartilage.

[This article presents several new concepts of the different roentgen appearance of ankylosing spondylitis in women and of the differential diagnosis from rheumatoid arthritis. It should be read in its entirety by those interested in these two conditions.]

Thirty-nine roentgenograms; 1 table.

THEODORE E. KEATS, M.D.
University of Missouri

Actual Problems in Contrast Myelography. K. Reinhardt. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 809–819, December 1955. (In German) (Strahleninstitut der Universitätskliniken im Landeskrankenhaus Homburg an der Saar)

One of the most serious complications of injecting iodized oil into the spinal canal is the formation of an oil granuloma in the lumbar sac. This condition can scarcely be remedied by any known method of treatment. Iodipin is more hazardous in this respect than Pantopaque. Pantopaque, being more fluid, is more likely to enter the basal cisterns, where granuloma formation simulates a cerebellopontine angle tumor. In so far as its local effect is concerned, Thorotrast is less apt to cause an immediate reaction but, since it is radioactive, the late formation of sarcoma must be considered.

The author favors Perabrodil, a water-soluble contrast medium, as the safest and best for myelography. While air or oxygen is still safer, the roentgenograms obtained with their aid are as a rule inadequate. The few anaphylactic deaths reported thus far with Perabrodil constitute a recognized hazard. With sedation and with the concomitant use of an antihistamine, untoward reactions should be negligible in frequency.

A major difficulty in myelography is the lack of correlation between orthopedic diagnosis of a ruptured intervertebral disk and its roentgen demonstration. A factor to be considered is that radiography is not always wrong and that multiple prolapses occur frequently on an anatomic basis but are seldom diagnosed neurologically. Further complications in demonstration of a prolapsed disk arise when arachnoiditis is present. Arachnoiditis may be produced not only by the persistent irritation of a ruptured disk but also by previous attacks of meningitis, by trauma, and by previous lumbar puncture.

Twelve roentgenograms; 2 tables.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

The Myelographic Appearance of Sacral Cysts. William B. Seaman and Leonard T. Furlow. J. Neurosurg. **13:** 88–94, January 1956. (Washington University School of Medicine, St. Louis, Mo.)

This paper is concerned with the roentgen appearance of cysts within the sacral spinal canal. These cysts usually occur at the junction of the posterior root and the dorsal ganglion and most commonly on the second and third sacral roots, although any of the sacral or

coccygeal roots may be involved and similar cysts have been seen on thoracic dorsal ganglia. Their pathogenesis is obscure. Various investigators have suggested that they result from splitting of the nerve root sheath, from arachnoidal proliferation, or as a result of nerve trauma with intraneural hemorrhage and cystic degeneration.

Roentgen examination may disclose an oval area of radiolucency in the sacrum, usually at the level of the second, third, and fourth sacral segments, and best visualized in the lateral view. This was seen in 3 of the 4 cases reported upon in this article. In addition, myelographic examination may disclose a communication between the subarachnoid space and the cyst, although this is not invariable. In the present series it was seen in 3 instances. In the absence of a communication, the cyst may displace the cul-de-sac laterally.

Sacral cysts may be associated with low back pain of sciatic type, and operative removal may result in relief of symptoms. However, in 2 of the cases reported here the finding was an incidental one, the patients being essentially asymptomatic.

Eight roentgenograms. RICHARD G. LESTER, M.D.
University of Minnesota

Osteoarthritis of the Cervical Spine. Stage and Treatment. John G. Kuhns. New England J. Med. **254:** 60–64, Jan. 12, 1956. (Boston University School of Medicine, Boston, Mass.)

The cervical spine is involved in at least 10 per cent of patients with osteoarthritis. Although sharp criteria are lacking, this troublesome affliction of the neck can be roughly divided into three stages, based on the degree of severity of the disease.

Clinically, Stage I is marked by pain, stiffness, and spasm of the antigravity muscles of the neck. Roentgen study shows minimal changes: early bony proliferation around the vertebral bodies and a slight loss in cervical lordosis. Treatment should include a well fitted collar that can be removed for the intermittent application of heat. Particular attention should be paid to the correction of postural defects. These patients do better if symptomatic foci of infection are eradicated.

In the moderately advanced cases, Stage II, the signs and symptoms are chiefly neurological, with radiating pains. Bizarre complexes may appear, since there are eight pairs of cranial nerves and three pairs of sympathetic ganglions communicating with the cranial nerves. Roentgenograms reveal greater bony proliferation about the vertebral margins with narrowing of the disks, particularly in the lower cervical spine. In addition to the measures outlined for Stage I, traction with or without tongs is indicated. Occasionally a neural foramen may be so narrowed that removal of the posterior portion of an intervertebral joint will be necessary for relief of symptoms. Rarely will cervical myelography reveal a protruding disk and therefore disk removal is not indicated. X-ray and ultrasonic treatment are occasionally helpful.

In Stage III, symptoms arise from the mechanical derangement of the vertebral bodies, which are markedly displaced, as well as from nerve irritation. Bony proliferation is extreme, there is reversal of the cervical lordosis, and the disks disappear, occasionally leaving Schmorl's nodules behind. Rarely there is associated osteoporosis with collapse of a body and marked displacement leading to severe neurologic symptoms. Treatment in the late stage is symptomatic, with a firm, snug collar which gives support to the chin and occiput. Traction may afford symptomatic relief, but surgery and x-ray treatment are rarely indicated.

Six roentgenograms; 1 table. SAUL SCHEFF, M.D.
Boston, Mass.

Vertebral Body Fusion for Ruptured Lumbar Discs. A Roentgenographic Study. Ralph B. Cloward. Am. J. Surg. **90:** 969–976, December 1955. (1013 Bishop St., Honolulu 13, Hawaii)

Vertebral body fusion was employed as treatment for ruptured lumbar intervertebral disks in 427 patients, 354 of whom were followed for six months or longer and evaluated by serial roentgenograms and clinical studies. Successful fusion as determined roentgenographically was accomplished in 97 per cent. The author's procedure incorporates disk removal, insertion of a homogeneous or autogenous interbody graft, and posterior interlaminar fusion with a large quantity of fine bone crumbs.

The roentgen criteria of fusion were: (1) no indication of movement of the fused joint on bending films; (2) increased density of the interbody grafts, with visible trabeculation across the intervertebral space; (3) solid bridging of bone overlying the lamina posteriorly. Two of these conditions had to be met before the spine was regarded as fused.

The average time for interbody fusion was 4.2 months as evidenced by serial films. Seven per cent of the interbody grafts failed to fuse. The fate of these grafts is discussed by the author. Contrary to experimental observations, they do not appear to undergo necrosis and absorption. In most cases they show first an increased density, with subsequent decalcification over a period of months or years until the graft and adjacent vertebral bodies appear uniformly dense. As a rule, the grafts maintain their size, shape, and position in the intervertebral space until healing is complete. The space was found to have been increased in width as a result of the graft in 42 per cent of the cases; the width was unchanged in 12 per cent. Grafts which were soft, with fatty cancellous bone and a thin cortical surface, became compressed and narrowing of the interspace occurred before fusion was complete. No difference in the behavior of the autogenous as compared to preserved homogeneous bone was observed roentgenographically, as to the rate of fusion and percentage of fusions and absorptions.

Changes in marginal osteophytes were noted, in that diminution in density and finally disappearance of spurs occurred following fusion.

The fate of the posterior bone chip and crumb grafts differed from that of the interbody grafts. In 14 per cent of the cases the bone chips disappeared completely; in 26 per cent there was very little new bone formation and the posterior fusion appeared weak. Five to eight months were required for roentgenographic evidence of good fusion posteriorly; this was two to five months longer than for interbody grafts. In 15 patients the posterior fusion was strong whereas the anterior fusion appeared weak.

Evidence of fusion of either the interbody grafts or the posterior grafts, or both, was obtained in 97 per cent of the patients.

Eleven roentgenograms; 1 table.

STEPHEN N. WIENER, M.D.
Mt. Sinai Hospital, Cleveland

The Indications for Tomography of the Hip Joints. P. Deák, A. Gazda, and G. Ragályi. Fortschr. a. d. Geb. d. Röntgenstrahlen **84:** 61–66, January 1956. (In German) (P. D. Péterfy S. u. 8–14, Budapest VII, Hungary)

Little has been written regarding tomography of the hip. The authors have been routinely employing this method of examination in early disturbances of the hip joint and have been able to make a correct diagnosis in lesions that could not be diagnosed by any other means.

Their routine procedure is as follows: First, a plain scout film is taken, with the central ray directed to a point at the intersection of the inguinal line with a horizontal line about two finger breadths above the symphysis. A narrow cone is used. For the planigraphic films, the focus-film distance is 100 to 120 cm., and the angle of deflexion is 60°. Films are taken in slim patients at cuts of 7 to 9 cm. and in heavier patients at 10 to 21 cm. For the visualization of the trochanters 1 or 2 cm. less is used.

Four cases are reported in which a correct diagnosis was made possible by tomographic examination. In the first case, the plain film showed only diffuse bone atrophy of the femoral head and neck, while the tomographic films revealed a sequestrum within a cavitation of the head which at operation proved to be of tuberculous origin. In another case the scout film demonstrated an indistinct lesion in the upper rim of the acetabulum, which proved on tomography to be an abscess cavity with a sequestrum. In the third case the plain film showed a bone defect with a sclerotic margin in the head of the femur, and only the tomograms indicated that the lesion had pierced the surface of the femoral head and was extending into the joint space. In the last case cystic lesions in the hip joint were apparent tomographically, though the only diagnosis permitted by the plain film was osteoarthritis. The films which are reproduced are excellent and quite convincing.

The authors suggest tomographic examination (1) for demonstration of erosion of the joint surface which cannot be plainly seen on the scout film; (2) for demonstration of primary foci within the bone and their localization, as well as sequestra and other processes that are hard to evaluate on the plain film; (3) for demonstration of bony ankylosis and of fine traumatic changes.

Eight roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

A Study of Experimental Trauma to the Distal Femoral Epiphysis in Rabbits. Lee T. Ford and J. Albert Key. J. Bone & Joint Surg. **38-A:** 84–92, January 1956. (L. T. F., Washington University School of Medicine, St. Louis, Mo.)

In order to determine which part of the epiphyseal cartilage is responsible for longitudinal growth of an extremity, the distal growth centers of 29 rabbit femora were subjected to experimental injuries. The experiments were performed unilaterally, so that a normal control femur was available in each animal for comparison.

It was found in 10 rabbits that when the peripheral portion of an epiphysis was damaged (by curettement), rather marked limitation of growth and deformity followed. In 8 rabbits a hole was drilled across the epiphyseal plate, and the central portion of the cartilage curetted out through the drill hole, leaving the peripheral cartilage intact. This caused more pronounced shortening of the femur. Broadening of the distal femur, which developed, simulated the appearance in chondrodysplasia. In 11 animals a simple drill hole was made across the center of the epiphyseal plate. This caused only mild to moderate growth interference.

It appears from these results that the central portion of the epiphysis plays the most active role in growth. However, if either the central or peripheral portion is damaged extensively, there will be premature bony fusion between the metaphysis and epiphysis.

Six roentgenograms; 4 photomicrographs; 3 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Non-Endocrine Dwarfism and Pseudoepiphyses. Richard Wagner. Am. J. Dis. Child. **91:** 6–13, January 1956. (20 Ash St., Boston 11, Mass.)

A syndrome characterized by dwarfism, retarded skeletal maturation, and congenital heart murmur is reported in 11 patients: 10 boys and 1 girl. The age range was from eighteen months to fifteen years, the 3 children who had reached puberty showing, in addition, sexual infantilism. Dwarfism was the chief complaint. Mental development was normal in all but one instance. The cause of the heart murmur was not determined. Cardiac catheterization and angiocardiography were not performed.

Bilateral pseudo-epiphyses of the proximal end of the second metacarpal was a frequent finding. Pseudoepiphyses differ from true epiphyses in that they appear early, grow rapidly, and coalesce precipitately and precociously. They appear at about two to three years of age, coalesce with the diaphysis at six to seven years, and at fifteen merge completely with the diaphysis.

Neither a cardiac anomaly nor an endocrinopathy could be demonstrated as the primary etiologic factor. A combination of genetic defects is postulated as the cause of the syndrome.

Six roentgenograms; 1 table.

J. E. CARLISLE, M.D.
Shreveport, La.

A Contribution to the Question of Congenital Disturbances of Subchondral Cartilaginous Ossification. H. Meisenheimer. Fortschr. a. d. Geb. d. Röntgenstrahlen **84:** 67–70, January 1956. (In German) (Nusplinger Strasse, Stetten a. K.M., Germany)

Liess, in 1954, reported disturbances of the cartilaginous ossification in the hands and in the feet of patients with Scheuermann's disease (Fortschr. a. d. Geb. d. Röntgenstrahlen **80:** 153, 1954). Inspired by these investigations, the author presents the case of a seventeen-year-old boy with Scheuermann's disease who had definite changes in the epiphyses of the fingers. Roentgenograms of the hands showed a narrowing of the epiphysis of the middle phalanx, with increased radiodensity, while the epiphyses of the proximal phalanx of the second and third fingers showed a central compression. The patient's father and 3 of 4 siblings showed similar disturbances in the epiphyses of the interphalangeal joints. The father showed, also, evidences of epiphyseal disturbances in the great toes. One of the brothers had Scheuermann's disease.

The author believes that the old assumption that Scheuermann's disease is merely an aseptic necrosis of the epiphyses of the vertebral bodies may have to be revised. A congenital disturbance in the subchondral

cartilaginous ossification may be a definite factor in the development of the condition.

Six roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

The Mechanism of Ankle Injuries. Barnard Kleiger. J. Bone & Joint Surg. **38-A:** 59–70, January 1956. (Hospital for Joint Diseases, New York, N. Y.)

This discussion of ankle injuries emphasizes the ligament tears which occur from lateral rotation of the foot (deviation laterally of the forefoot relative to the long axis of the tibia), eversion and inversion of the foot (rotation of the foot and heel around the long axis of the calcaneus), and vertical compression of the ankle.

For adequate assessment of injury to the ankle ligaments, the author advises conventional anteroposterior and lateral roentgenograms and anteroposterior views with the foot in lateral rotation and with the foot inverted.

If lateral displacement of the talus is seen, with widening of the mortise and of the space between the talus and the tibial malleolus, there is said to be lateral ankle instability. This results from lateral rotation of the foot, which may cause tearing of ligaments and displacement of the fibula from its tibial groove. The ligament injuries of eversion can also produce lateral instability with or without diastasis.

The characteristic fracture of the tibia resulting from eversion is a transverse or slightly oblique fracture of the medial malleolus. These forces also cause a spiral fibular fracture whose proximal end is located posteriorly and whose distal end is situated anteriorly. This is not seen well on an anteroposterior film, but shows best on lateral or oblique views. In contradistinction, foot invesion sometimes produces a spiral fibular fracture which has the proximal end located posterolaterally and its distal end anteromedially. This fracture is best demonstrated in the anteroposterior projection.

Following inversion injuries, lateral ligament tears are reflected by inward tilt of the talus. This is especially well shown on anteroposterior films made with the foot in inversion. If the lateral ligaments do not rupture, the fibula may be fractured transversely at or below the level of the ankle joint. The characteristic tibial fracture of inversion is a longitudinal split which separates the medial malleolus and may displace it medially.

Fractures of the posterior lip of the tibia at the ankle are due either to lateral rotation forces or to compression by the talus when it is forced upward and backward. They cannot usually be differentiated roentgenographically.

The bony changes following compression injuries at the ankle level depend upon the position of the foot at the time the force is applied. Varying degrees of spread of the mortise and fractures of the articular surface of the tibia are the most common findings.

Thirty roentgenograms; 3 photographs; 11 diagrams.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

OBSTETRICS AND GYNECOLOGY

Ureteral Stenosis and Hydronephrosis Due to Carcinomatous Infiltration and Irradiation Induration of the Parametrium in Cervix Carcinoma. Erich Buchmann. Strahlentherapie **99:** 20–38, January 1956. (In German) (Röntgen- u. Geschwulstinstitut und der Geburtshilflich-Gynäkologischen Klinik im Rudolph Virchow-Krankenhaus, Berlin, Germany)

Intravenous pyelograms in 181 women with cervical carcinoma were evaluated over an observation period of five years. In a considerable number of cases (37 per cent) hydronephrosis was present before the beginning of therapy. Of Stage 2 cases with no involvement of the parametrium demonstrable on palpation, 30 per cent showed urinary stasis. All these patients died within two years with or without treatment. The author's conclusion is that intravenous pyelography should be routine in cervical cancer because of the frequency of hydronephrosis and diagnostic errors in staging. The importance of pyelographic studies at regular intervals after completion of irradiation therapy is also stressed.

On the basis of topographic roentgenograms, dosimetry on cadavers, microscopic examinations, and clinical observations, a thorough discussion of the etiology and pathogenesis of hydronephrosis in these cases is undertaken. It may be due to:

(1) The neoplasm itself:
  (*a*) Compression of the ureteral lumen
  (*b*) Cancerous infiltration of the ureteral wall
  (*c*) Metastasis *via* the ureteral lymphatics.
(2) Irradiation:
  (*a*) Acute and usually transitory edema of the ureteral mucosa and inflammatory parametrial exudate
  (*b*) Replacement of the tumor cells by fibrosis during the healing process, with callous induration and stenosis of the ureters
  (*c*) Chronic periureteritis and circumscribed ureteritis with cicatricial stricture.

There were many women who, although completely cured of cancer, died from uremia caused by irradiation induration of the parametria, with ureteral stenosis and stricture. Contrary to stasis caused by carcinoma, these cases offer a favorable prognosis when diagnosed in time, since they present a vital surgical indication to secure unobstructed urinary excretion. Their early recognition and treatment are discussed in detail. The complications observed after a combination of intracervical radium insertion with intravaginal and external x-ray irradiation can be avoided if an individual treatment plan is laid out. The saturation technic with intravaginal x-ray therapy delivers from 5,000 to 20,000 r to the ureters and is usually responsible for the ureteral complications. They are more frequent and of greater clinical significance than the often discussed complications involving the urinary bladder and the rectum.

The author recommends reduction of the dose administered by intravaginal x-ray therapy and extensive use of pyelographic procedures, with early surgical measures to obtain urinary flow.

Fourteen roentgenograms; 3 photographs; 6 photomicrographs; 3 tables.

HERBERT C. POLLACK, M.D.
Chicago, Ill.

THE GENITOURINARY SYSTEM

Abdominal Venography in Urological Diagnosis. Joseph J. Kaufman, Donald E. Burke, and Willard E. Goodwin. J. Urol. **75:** 160–168, January 1956. (VA Hospital, Los Angeles, Calif.)

Roentgen visualization of the inferior vena cava has

limited indications, but it may provide information of considerable importance in urological diagnosis. Renal and adrenal tumors frequently involve the vena cava by direct venous extension of tumor thrombus or by external compression: Testicular tumors commonly metastasize to retroperitoneal lymph nodes and cause compression or deformity of the inferior vena cava. Anomalies of the vena cava, on the other hand, may involve the ureter, as in retrocaval ureter.

The authors suggest the following indications for abdominal venography: (1) to confirm suspected caval obstruction in the presence of ascites, dilated superficial veins, and leg or scrotal edema; (2) to ascertain the presence of caval disease when there are no clinical signs or symptoms to suggest obstruction (renal, testicular, adrenal, and possibly bladder and prostatic cancers); (3) to detect tumor thrombus formation in the vena cava when advanced renal and adrenal neoplasms are known to exist; (4) to demonstrate the course of the vena cava in relation to the ureter when retrocaval ureter is suspected; (5) to aid in diagnosis of retroperitoneal tumors, such as lymphomas or metastatic tumors when the primary source is unknown; (6) to localize retroperitoneal tumors, primary or metastatic, in order to plan x-ray therapy.

The methods practiced by the authors included bilateral percutaneous femoral vein puncture, translumbar vena cava puncture, and percutaneous femoral vein catheterization. Blood pressure cuffs on the thighs and the Valsalva maneuver have been employed to concentrate the contrast medium in the abdominal veins during x-ray exposure. Usually 25 c.c. of Urokon Sodium 70 per cent is injected simultaneously in each femoral vein.

The authors have obtained venacavagrams in 50 cases and, except for transient discomfort associated with extravasation of the medium outside the femoral vein in 20 per cent of the patients, they have seen no untoward effects. They consider the procedure to be as safe as intravenous urography. The only contraindications are sensitivity to the contrast medium and the presence of active thrombophlebitis of the leg or pelvic veins.

Six case reports are included.

Seven roentgenograms; 2 drawings.

ALFRED O. MILLER, M.D.
Louisville, Ky.

Cystography in Children. Eugene C. St. Martin, James H. Campbell, and Claude M. Pesquier. J. Urol. **75:** 151–159, January 1956. (E. C. St. M., 940 Margaret Place, Shreveport, La.)

The usual indication for urologic investigation in the infant or child is some symptom of vesical dysfunction. Routine cystoscopy and pyelography may not give an accurate picture of vesical function. Cystography is more likely to demonstrate enlarged bladders, trabeculation, cellules, residual urine, and vesicoureteral reflux.

The patient is catheterized after voiding, and the bladder is then filled with contrast medium (5 per cent sodium iodide) by gravity until the patient feels full or the liquid level begins to waver up and down in the barrel of the syringe. A film is made which is termed the "gravity cystogram." The catheter is then removed and the patient is again urged to void. A film made during voiding is taken in the older child. Immediately after micturition is complete, a "post-voiding cystogram" is obtained. An emptying film is taken if reflux demonstrates a tortuous ureter. The remainder of the urological examination, cystourethroscopy and pyelography, is completed subsequently.

In ten months a total of 100 children (60 girls; 40 boys) were given complete urological examinations. The gravity cystogram was of value in determining bladder size, but whereas trabeculation was seen 70 times endoscopically, it was found only twice in the gravity cystogram. The post-voiding film showed trabeculation in 22 patients with residual medium in whom there was also endoscopic evidence of trabeculation. Two patients had a diverticulum of the bladder.

Vesicoureteral reflux was demonstrated in 20 children. Fourteen of these cases were readily detected in the gravity cystogram and the additional 6 cases were demonstrated on the voiding or post-voiding film. The incidence of reflux was 50 per cent higher when the act of micturition was initiated and the necessary intravesical pressure of voiding against an obstruction was developed. The immediate post-voiding cystogram is considered most contributory for the detection of residual urine and serious vesicoureteral reflux.

Nine roentgenograms. ALFRED O. MILLER, M.D.
Louisville, Ky.

Renal Papillary Necrosis. J. C. Christoffersen and Kjeld Andersen. Acta radiol. **45:** 27–41, January 1956. (Bispebjerg Hospital, Copenhagen, Denmark)

The etiology of renal papillary necrosis is obscure. The sparsity of the blood supply and its unique pattern of distribution are cited as possible causative agents. The frequency of associated sclerotic vascular involvement suggests that this may be a contributing factor. The presence of a pre-existing pyelonephritis argues for a bacterial origin.

The diagnosis of the disease is difficult and is not often made antemortem. The most common signs and symptoms are dysuria, fever, chills, nausea and vomiting, and flank pain. Sometimes oliguria and anuria are encountered. Finally, hypertension and azotemia may develop. Death may supervene quickly or the condition may become chronic, and opportunity for palliation or cure may be afforded.

Laboratory studies may demonstrate the presence of staphylococci, *Esch. coli*, streptococci, or proteus organisms in the urine. The tubercle bacillus and actinomyces have also been reported as causative agents.

Günther (Ztschr. f. Urol. **41:** 310, 1948) distinguished between papillary and medullary necrosis and described four stages of each. There were no medullary necroses in the series of 8 cases seen by the present authors, but all stages of papillary necrosis were represented.

Intravenous and retrograde pyelographic studies should be done on all cases, as one method often succeeds where the other fails. Calyceal deformity may suggest the diagnosis. The authors describe two principal findings. One is a ring-like area of opacity in a calyx, surrounding a zone of lesser density (Stage III). The other is the replacement of the normally cup-shaped calyx by a bean-sized cavity with a fairly well defined, peripherally convex margin (Stage IV). The condition must be differentiated from fornix-sinus backflow, pyelolymphatic and pyelovenous backflow, and calyceal diverticulum.

The value of detailed knowledge of both normal and pathologic anatomy in enabling one to reach a correct

diagnosis is emphasized. Both gross and microscopic changes are described in considerable detail. One or all of the papillae may be involved and the disease may be unilateral or bilateral.

The prognosis is grave but the outcome is not invariably fatal. Some patients are benefited by resection of the affected portion of the kidney or a nephrectomy when indicated.

The authors tabulate the observations in their 8 cases and report 2 histories in detail. These cases differed from those previously appearing in the literature in that the patients (all women) were younger. Only 1 had diabetes and 2 obstructive uropathy, both of which are commonly associated with this condition. The necrosis seems to have been isolated and none of the cases terminated fatally.

Seven roentgenograms; 1 figure; 1 table.

H. C. JONES, M.D.
Grand Rapids, Mich.

Observations on Ureteral Obstruction and Contractility in Man and Dog. John A. Benjamin, Joseph J. Betheil, Victor M. Emmel, George H. Ramsey, and James S. Watson. J. Urol. **75:** 25–42, January 1956. (University of Rochester School of Medicine and Dentistry, Rochester, N. Y.)

A few clinical observations on ureteral obstruction are reported but the greater part of this paper is devoted to cinefluorographic studies on dogs. After retrograde filling of the ureter, pelvis and calyces of a normal dog with 30 per cent Urokon, ureteral contractions were recorded by means of cinefluorography. The contrast medium is returned from the kidney pelvis to the ureter in quick, intermittent spurts or jets. Ureteral contraction waves, forceful enough to obliterate the lumen, then sweep down the ureter to the bladder. In some cases the traveling contraction is only a few centimeters in length, and the lumen opens up again behind it, apparently in response to a second ejection of contrast medium from the kidney pelvis. In other cases the entire length of the ureter may remain contracted below the advancing wave front, so that nearly all the ureteral contents are expelled. Residual medium is seen in the pelvis and calyces. The absence of the contrast medium in the ureter, at the site of contractions, indicates that the peristaltic waves are sufficiently forceful to obliterate the lumen. There was no evidence in these studies that the normal dog ureter was dilated, elongated, or enlarged during the contraction movements of the ureter, or that the catheter produced abnormal contraction waves.

When the ureter was minimally obstructed by placing an aluminum band near the ureterovesical juncture, moderate ureteral enlargement, elongation, and kinking could be produced. The elongation and bending under these conditions usually developed near the ureteropelvic juncture. The contraction waves, however, are quite similar to those of the normal ureter just described. In this instance the wave was long and appeared pinched off at either end. Again, as in the normal ureter, the medium at the site of contraction was completely removed from the ureteral lumen. If the obstruction was more severe, the dilatation, elongation, and angularity were correspondingly increased. When the ureter is markedly distended as a result of obstruction, one may not see contraction waves during cinefluorography, or the waves will be short and sluggish, as seen in the x-ray motion pictures.

In one experiment one-half of the circumference of the ureter was removed for a distance of 5 cm. and the defect bridged by a polyethylene tube. The ureter was then allowed to regenerate over this tube. Five months later x-ray motion pictures were made. Active ureteral contractions were seen above and below the site of regeneration. Of interest was the development of a diverticulm at the site. Motion-picture studies showed no evidence that this diverticulum could contract. Later when it was sectioned, it was found to be devoid of muscle fibers. In other experiments, a portion of the ureter was completely excised for a distance of 5 cm. and the defect bridged by a polyethylene tube. Contraction waves were seen both above and below the ureteral defect, but the wave did not appear to follow in sequence or to be synchronous.

The authors also studied histologic sections of the ureteral wall and carried out perfusion experiments and enzyme studies, which are briefly reported.

Thirty-eight illustrations, including 21 roentgenograms.

ALFRED O. MILLER, M.D.
Louisville, Ky.

TECHNIC

High Tension Switch Tube for Roentgenography. Charles T. Dotter and Thomas H. Rogers. Am. J. Roentgenol. **75:** 83–90, January 1956. (C. T. D., University of Oregon Medical School, Portland 1, Ore.)

The authors describe a new device which makes possible exposures of 0.001 to 0.005 second. It consists of a high-voltage tetrode operated in series with the diagnostic x-ray tube. The typical factors as given for an 11-cm. anteroposterior chest film are 92 kvp, 1,075 ma, 36 in. target-film distance, and 0.001 sec. It is not quite clear whether the 500-ma generator was overloaded to give the 1,075 ma.

While the authors argue that rates of 12 exposures per second [as available in the Elema biplane apparatus] are probably not necessary in angiocardiography, they demonstrate an interatrial septal shunt which "was small and showed only on this film." It would then seem that, even with the short exposure time and slow exposure speed, the demonstration of this defect was fortuitous!!

Eleven roentgenograms; 2 oscillograms; 1 photograph; 2 diagrams; 1 table.

LAWRENCE A. DAVIS, M.D.
University of Louisville

Cinefluorography: Technical Refinements. S. A. Weinberg, J. S. Watson, and G. H. Ramsey. Am. J. Roentgenol. **75:** 63–68, January 1956. (G. H. R., Strong Memorial Hospital, Rochester 20, N. Y.)

A number of recent developments in the field of x-ray motion studies are reported.

(1) A film projector, originally designed for football coaches for post-game analysis, has been modified to afford slow, flicker-free cinefluorographic projection and to permit instantaneous switching from continuous to single frame operation.

(2) Cinefluorography and conventional cinematography have been combined so that the subject will appear partly transparent (penetrated by roentgen rays) and partly solid. This is accomplished by replacing the fluorescent screen of the cinefluorographic unit with a pane of glass or Lucite and attaching to

this a smaller screen covering only a portion of the camera field. A practical application has been the fluoroscopic filming of the internal organs of speech, while the head and face are seen as in the usual photograph. Such an illustration accompanies the publication.

(3) Two motion-picture cameras have been adapted to high-speed lenses, by relocation of the shutter in one instance and the use of two shutter blades in another.

(4) By revolving the subject continuously between the roentgen-ray source and fluoroscopic screen and using a twin projector or a single channel projector with tandem apertures, a stereoscopic illusion is produced superior to that obtained with side-by-side tubes and an alternate-frame stereoscopic projector.

(5) A 70-mm. cinefluorographic unit has been adapted to useful cineroentgenographic filming of extremities at a rate of 15 frames per second without excessive roentgen dosage. A set of frames from an examination of the wrist by this means is reproduced, showing remarkable osseous detail.

Four roentgenograms; 5 photographs.

DALE W. UNDEM, M.D.
University of Louisville

Stereofluoroscopic Spot Films. E. S. Kerekes. Am. J. Roentgenol. **75:** 141–143, January 1956. (2917 S. Boston Court, Tulsa 5, Okla.)

The author advocates the use of stereoscopic films taken during fluoroscopy in those procedures where little or no physiologic motion occurs, and where compression devices are not necessary. Stereoscopic spot-films are made by shifting the entire stereoscopic carriage after the first spot of a pair is taken. After processing, the film is cut, separating the stereo pairs. They are then examined in the usual fashion.

Such a method is described for use with conventional equipment. It has proved most beneficial in contrast studies of the colon, in postoperative cholangiography, bronchography, and myelography.

One pair of stereo spot-films; 1 diagram.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

A Simple Device for Stereoscopic Viewing of Films. E. S. Kerekes. Am. J. Roentgenol. **75:** 140, January 1956. (2917 S. Boston Court, Tulsa 5, Okla.)

A simple device for stereoscopic viewing of films is described. It consists of a front surfaced mirror 2.5 × 3 inches. Two standard view boxes are necessary, and a stand or support to eliminate trembling of the hand-held mirror.

A diagram of the application of this simple inexpensive method of stereoscopy is presented. With this procedure eye-crossing and ocular muscle strain are avoided.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

Roentgen Examination of Old and New Trauma of the Spine with the Ultra-Fine Focus Roentgen Tube. Claude D. Baker, Frank E. Lane, and Everett L. Pirkey. Am. J. Roentgenol. **75:** 144–148, January 1956. (E. L. P., Louisville General Hospital, Louisville, Ky.)

The authors discuss the advantage of geometric enlargement of the roentgenographic image of the spine by the use of an ultra-fine focus tube. Anteroposterior, lateral, and oblique films are taken of the desired part at a 42-inch target-film distance, with the patient on an elevated platform with a plastic window above the table top and the spine about half way between the tube and film.

The geometric method of enlargement makes use of the divergence of the beam of roentgen rays. The degree of enlargement is the ratio between the target-film distance and the target-object distance A double-focus rotating anode tube is used, with a 1.5 mm. and a 0.3 mm. focal spot. This should not impose any undue financial burden on a large roentgen department, since the 1.5 mm. focal spot can be used for routine work and the smaller spot for special procedures.

This technic has been of definite aid in the differential diagnosis between old and new trauma, thus sparing the patient the use of a body cast and many hospital days. It likewise has been an aid in medicolegal cases by enabling the radiologist to arrive at a more definite opinion.

ROBERT H. LEAMING, M.D.
Memorial Center, New York

RADIOTHERAPY

The Construction and Measurement of Beta-Ray Applicators for Use in Ophthalmology. W. K. Sinclair and N. G. Trott. Brit. J. Radiol. **29:** 15–23, January 1956. (Institute of Cancer Research, Royal Cancer Hospital, London, S. W. 3, England)

In connection with their treatment of certain eye diseases with beta radiation, the authors developed a new type applicator, which they describe.

A contact lens type of device seemed to be more practical than the long-handled plaque holder used heretofore, and initial experiments were performed with molds of phosphorus 32 and Bakelite. More satisfactory molds were eventually developed from polythene, within which were embedded thin sheets of foil of strontium 90 (in equilibrium with yttrium 90), which has a twenty-year half-life.

After trials with molds of different sizes and shapes, the number of types of molds was reduced to 4, all of the same basic size but with varying distributions of the radioactive foil.

Scintillation probe measurements of dose rate at various points on the surfaces of the applicators were carried out and rather meticulously compared with flat-plane standards and absolute measurements made with a shallow ionization chamber. Depth-dose measurements and distribution were also carefully studied.

It was decided that dose rates at various points on the applicator surfaces should always be within plus or minus 10 per cent of the mean value. Any applicators having greater variation were rejected. Surface dose rates for these applicators are in the neighborhood of 100 rad/minute.

Isodose curves for the different types of applicators show that it is possible either to irradiate the entire area beneath the applicator uniformly or to irradiate one part of tissue more heavily than elsewhere. The applicators described should suffice for most clinical purposes, but other distribution plans seem to be readily practicable.

Twelve figures; 1 table.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Aimed Deep Therapy with Fixed Fields. F. Gauwerky. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 802–808, December 1955. (In German) (Strahleninstitut des Allg. Krankenhauses St. Georg, Hamburg, Germany)

For good therapy, whether by rotation or by fixed-field methods, the first requirement is the recognition of the relationship of the disease process to the surface of the body. If, in addition, it is desired to protect the surrounding tissue by the use of small fields, correct beam direction is essential. Despite recent popularity of rotation therapy, most patients must still be treated through fixed fields, because of the equipment available.

Control of beam direction is of paramount importance, as has been recognized in the Anglo-Saxon laboratories. In the case of vertical therapy to a palpable tumor, with the patient recumbent, the problem of direction is negligible. Control of the beam may be obtained both by simultaneous fluoroscopy with the therapy tube and by simultaneous radiography, also with the therapy tube. For daily use, any aiming device is practical. The author has found the back pointer and the pin-and-arc apparatus to be quite applicable with a little practice.

For therapy with the patient upright, the back pointer is the better. The first step is the localization of the tumor radiographically in two directions. A plaster shell is then constructed to fit the patient, and on this the beam direction is determined by means of a second set of roentgenograms. The fields are marked on the shell. The patient is irradiated through the shell, which reduces the calculated dosage by 5 per cent, by reason of the intervening plaster. The back pointer is fixed to the roentgen tube.

For fixed-field therapy with the patient recumbent, the pin-and-arc device is recommended. The depth of the tumor is determined by anteroposterior and lateral roentgenograms taken with the patient in the position in which the deep therapy will be administered. A transverse body-section is constructed on paper, and on this the field directions are charted. The base points for the pin-and-arc device are transferred from this chart to the patient. The field sizes are also outlined on the patient's body.

Four photographs; 2 diagrams.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Thymic Neoplasms. Donald B. Effler and Lawrence J. McCormack. J. Thoracic Surg. **31:** 60–77, January 1956. (Cleveland Clinic Foundation, Cleveland, Ohio)

Thymic neoplasms may for practical purposes be classified as lymphomatous or carcinomatous. They are unpredictable and erratic in behavior, and on histologic grounds alone it is difficult to differentiate between benign and malignant thymoma. The authors, who present 19 cases, feel that all are potentially malignant.

It is also impossible pathologically to distinguish between the tumors of patients with and those without myasthenia gravis. This condition is related to thymoma in some way not presently understood, and it may be seen with either the benign or malignant form. Histopathologic findings have little value in prognosis.

The clinical and pathological features of the cases are presented in a table which shows that most of the non-resectable lesions in this series received benefit from radiation therapy. The tumor dose was usually carried to about 3,000 r.

Although the response cannot be predicted, the authors feel that every patient with thymoma should be treated with irradiation, either to the thymus or to the mediastinum postoperatively. If possible, operative removal prior to radiation therapy is preferable.

Nine roentgenograms; 6 photomicrographs 4 photographs; 1 drawing; 3 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Wilms's Tumour: Its Treatment and Prognosis. L. Stuart Scott. Brit. M. J. **1:** 200–203, Jan. 28, 1956. (Western Infirmary, Glasgow, Scotland)

The commonest tumor of the urinary tract in infancy and childhood is Wilms' tumor, with an overall mortality of about 80 per cent. The best results are obtained in patients admitted for treatment immediately upon appearance of the first symptom, who receive little handling before surgery. Prompt nephrectomy and intensive immediate postoperative deep x-ray therapy are recommended. A wide transperitoneal or transthoracic exposure of the kidney permits early ligation of the hilus, wide dissection of the adjacent fatty tissue, and delivery of even a large tumor without the necessity of preoperative irradiation.

Frequent leukocyte counts are necessary during irradiation, since the white blood cells are extremely vulnerable in childhood. Children of two years of age can tolerate from 1,000 to 2,000 r (tissue dose) without serious effects on the bone. More than 2,000 r produces retardation of bone growth at any age. A tissue dose of less than 1,000 r seldom causes permanent gross vertebral damage.

Several writers have reported apparent cures following irradiation of pulmonary metastases. The majority of recurrences and metastases appear within a year of treatment but metastasis may occur as late as five years postoperatively.

Objection to preoperative irradiation is based on the additional time provided for the tumor to liberate cells into the blood stream, thus leading to metastases.

Prognosis is gravely affected by hematuria, which denotes involvement of the renal pelvis. Age is also a factor: whereas the overall survival is about 20 per cent, the rate for children of over twelve months is only about 9 per cent.

One photomicrograph; 1 photograph; 1 graph; 2 tables.

DONALD DEF. BAUER, M.D.
Coos Bay, Ore.

Ankylosing Spondylitis. A Review. C. Bruce Perry. J. Fac. Radiologists **7:** 149–154, January 1956. (University of Bristol, Bristol, England)

The author summarizes the non-radiologic aspects of ankylosing spondylitis. The disease is essentially one of young adult males, and the usual onset is between eighteen and twenty-five years of age. There is a striking familial factor.

The etiology of ankylosing spondylitis is unknown. The theories of gonorrheal etiology have been discarded. The relationship between ankylosing spondylitis and rheumatoid arthritis is still a perplexing one. [In this connection, see the abstract of a paper by Middlemiss, p. 782.] In Great Britain it is generally agreed that the conditions are quite separate, the basis of this view being (1) the different sex incidence; (2)

the radiologic differences; (3) the absence of streptococcal and sheep red cell agglutinins in spondylitis; (4) the difference in type of joint affected, even where peripheral joints are involved in spondylitis; (5) the absence of subcutaneous nodules; (6) the histologic features. It is of interest that iritis occurs in well over 10 per cent of patients with ankylosing spondylitis.

The onset of spondylitis is usually insidious and it is often years before the real nature of the symptoms is recognized. The usual early symptoms are inconstantly recurring pains in the low back, the buttocks, and in the thighs. In about 10 per cent of the patients, however, the earliest symptom may be swelling and pain in a peripheral joint—usually knee or ankle—which gradually subsides. During the acute phase of the disease the pathologic process may extend into the larger proximal peripheral joints, particularly the hips. This seems to be a rather different process from the involvement of the peripheral joints sometimes seen in the early phase, since it leaves permanent changes. The disease spreads, with gradually increasing stiffness and pain extending up the spine and affecting one or more peripheral joints until the patient may be almost immobilized. Even a temporomandibular joint may be involved. Whatever the mode of the onset and however rapid or slow the progress of the disease, it may show arrest at any stage.

The role of x-ray therapy in ankylosing spondylitis is not clear. It is difficult, if not impossible, at the moment to decide whether radiotherapy really arrests the progress of the disease or not. There is no doubt that in the majority of cases it will relieve very considerably the acute pain and discomfort. The author suggests that repeated small doses of low-voltage radiation may actually be as beneficial as the modern method of large dosage and high voltage.

Five photographs. THEODORE E. KEATS, M.D.
University of California, S. F.

RADIOISOTOPES

A Quantitative Autoradiographic Study of Radioiodine Distribution and Dosage in Human Thyroid Glands. W. K. Sinclair, John D. Abbatt, Helen E. A. Farran, Eileen B. Harriss, and L. F. Lamerton. Brit. J. Radiol. **29:** 36–41, January 1956. (Institute of Cancer Research, Royal Cancer Hospital, S. W. 3, London, England)

After giving radioactive iodine there is wide variation in the radiation dose received by tissues at various points within the thyroid gland. Several clinical conditions also present non-uniform activity patterns throughout the gland. This report represents an attempt at quantitative measurement of such dose variations.

Contact autoradiographs were made of the tissues removed by thyroidectomy from 39 patients who were preoperatively given 100 microcuries of I^{131} orally. Measurements of the densities of the blackened portions of the autoradiographs were then made. In addition, beta-ray standard calibration films were made by exposing films to a solution of I^{131}. A curve was then prepared which permitted translation of the amount of autoradiographic blackening directly into terms of specific activity, once the time of exposure became known.

Comparison with direct scintillation counter readings on the surgical specimens showed good agreement, and there also was good correlation between the autoradiographic findings and the histologic and functional pictures.

The ratio between the maximum blackening and mean blackening found on each autoradiograph was tabulated for various clinical diseases of the thyroid. There was found to be wide variation in the value of the ratio for each group, especially in thyroid carcinoma and in lymphadenoid goiter. The high ratios obtained in the latter condition seem particularly significant. If such patients were to be given small tracer or therapeutic amounts of radioiodine, certain areas might receive sufficient radiation to alter function seriously and possibly to produce undesirable late effects.

Twelve figures; 2 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

The Value of Radioactive Iodine Uptake and Protein-Bound Iodine Estimations in the Diagnosis of Thyrotoxicosis. William H. Beierwaltes. Ann. Int. Med. **44:** 40–51, January 1956. (University Hospital, Ann Arbor, Mich.)

This paper reviews the utility of I^{131} uptake studies and protein-bound iodine (PBI) estimations in the diagnosis of thyrotoxicosis. Frequently the employment of these tests is unnecessary, since the diagnosis can be established by clinical observations, basal metabolic rates, and serum cholesterol levels. In threshold cases, however, I^{131} thyroid tracers and PBI determinations are an asset.

The most frequent source of error in interpretation of thyroid uptake and PBI determination is the prior administration of iodine, in the form of Lugol's solution or one of the radiographic contrast media. The effects of antithyroid drugs, thyroiditis, and pregnancy are also to be taken into account. A person with exophthalmic goiter receiving iodides has a slow I^{131} uptake, whereas the PBI may be elevated. In thyrotoxicosis under treatment with propylthiouracil both the I^{131} uptake at twenty-four hours and the serum PBI may be normal. The euthyroid patient with a larger goiter may show an increased I^{131} uptake by virtue of the volume of the thyroid tissue available to pick-up I^{131}. In pregnancy, the PBI and basal metabolism rate are commonly elevated, but the serum cholesterol level rises rather than falls, as would be expected if true thyrotoxicosis were present.

In uncomplicated congestive failure, the basal metabolic rate may be elevated and the serum cholesterol values lowered, while the I^{131} uptake and serum PBI estimates remain normal. If, however, the congestive failure is incident to thyrotoxicosis, the serum PBI values may be falsely lowered by the administration of mercurial diuretics. Similarly in leukemia and polycythemia, clinical symptoms suggesting hypermetabolism with an elevated basal metabolism and lowered serum cholesterol level may be obtained, but normal I^{131} uptakes and serum PBI values will exclude thyrotoxicosis.

Acromegaly and pheochromocytoma may be complicated by elevated basal metabolic rates, but normal

I^{131} uptake and serum PBI values will show the thyroid function to be normal. Alcoholic patients may have an elevated I^{131} uptake without clinical hyperthyroidism. Ingestion of excessive quantities of desiccated thyroid may result in clinical hyperthyroidism, an elevated PBI and basal metabolic rate, and lowered serum cholesterol (thyrotoxicosis factitia). The I^{131} uptake values, however, will be subnormal, since the ingestion of thyroid depresses the pituitary output of thyroid stimulating hormone (TSH). There is a reverse situation when a general clinical state of hypothyroidism is associated with an elevated I^{131} uptake and serum PBI. This is presumed to be due to an overactive thyroid gland losing excessive quantities of PBI that is not metabolically active thyroid hormone.

Nine charts.

JOHN W. WILSON, M.D.
University of Texas, Dallas

Alterations in Thyroid I-131 Uptake, Basal Metabolic Rate and Serum Cholesterol Following Treatment of Hyperthyroidism with Radioactive Iodine. Value in Early Prediction of Success or Failure of Therapy. Alvin L. Schultz and Leslie Zieve. Am. J. Med. **20:** 30–41, January 1956. (University of Minnesota, Minneapolis, Minn.)

The purpose of this study was to develop criteria by which the results of I^{131} therapy might be predicted shortly after administration. Sixty-six patients with hyperthyroidism were given I^{131} and were followed for varying periods up to seventy-nine weeks. Examinations, made every six to nine weeks, included clinical appraisal, basal metabolic rate, total serum cholesterol, thyroid I^{131} uptake, and, in a few cases, protein-bound iodine determinations. The chief value of these function studies appears to lie in the early post-therapy period, where results guide one as to whether or not treatment should be reinstituted.

Shortly after treatment, the thyroid uptake gives a fair estimate of the amount of radiation injury. At this time, basal metabolism, cholesterol, and protein-bound iodine determinations indicate, in a general way, the quantity of circulating thyroid hormone present.

Six to nine weeks later, the thyroid uptake reflects the eventual clinical result fairly reliably. The basal metabolism and protein-bound iodine determinations also are reasonably accurate in reflecting the ultimate course of the disease. The clinical status at this time is apparently a less dependable criterion. The serum cholesterol is chiefly of corroborative value.

The changes in any one test are not sufficiently consistent from patient to patient for complete dependability, and the combination of all seems more reliable.

Ninety-six per cent of those in this series in whom the first post-therapy evaluation indicated hyperthyroidism ultimately proved to be treatment failures. Fifty-eight of the 66 patients eventually obtained remission of symptoms (a number received more than one dose); and 14 became significantly hypothyroid.

Two figures; 4 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

An Evaluation of Various Factors Influencing Treatment of Metastatic Thyroid Carcinoma with I^{131}. Farahe Maloof, Austin L. Vickery, and Betty Rapp. J. Clin. Endocrinol. & Metab. **16:** 1–27, January 1956. (Harvard Medical School, Boston, Mass.)

Observations on a group of 21 selected patients with metastatic thyroid carcinoma are reported. Surgical total thyroidectomy was performed in 15 of the 21 patients. In 7 of this number an uptake of I^{131} was induced in the metastases and in 5 others it was increased. The administration of antithyroid drugs to 14 of the 21 patients increased the uptake by metastases in 8. This increased uptake may, however, be outweighed by the growth stimulus imparted to the metastases.

Functional and histologic variations in metastases in the same patient may also defeat the attempt to treat thyroid carcinoma successfully with I^{131}. Histologic and autoradiographic studies showed a marked difference in uptake and response to I^{131} in adjacent portions of biopsy specimens.

To assess the possible general bodily effects of administration of large doses of I^{131}, an evaluation was made of pituitary, adrenal, gonadal, and hepatic function in some patients. Changes in the hematopoietic system were also followed. Complications of I^{131} treatment were relatively insignificant except for changes in the hematopoietic system. Such changes may return to normal during a program of desiccated thyroid therapy and discontinuance of I^{131}.

Desiccated thyroid, but not testosterone, appeared to be of value in controlling the growth of thyroid metastases which had been sensitive to I^{131} treatment.

Six roentgenograms; 1 autoradiograph; 1 photograph; 5 photomicrographs; 9 graphs; 3 tables.

ALVIN SEGEL, M.D.
Cleveland City Hospital

Leukaemia Following Radioiodine Treatment of Hyperthyroidism. E. E. Pochin, N. B. Myant, and B. D. Corbett. Brit. J. Radiol. **29:** 31–35, January 1956. University College Hospital Medical School, London, W. C. 1, England)

The authors report a fatal case of leukemia in a 41-year-old woman who had previously received treatment for hyperthyroidism with radioactive iodine. Complete relief of the symptoms of hyperthyroidism followed administration of 7.1 mc of radioiodine over a five-month period. Approximately eighteen months later acute lymphoblastic leukemia developed.

It was estimated that the liver had received about 100 rep, the thyroid about 6,200 rep, and the blood about 10 rep. The cervical tissues outside the thyroid were thought to have received about 75 rep.

All things considered, it seems unlikely that the radioiodine treatment was relevant to the subsequent leukemia. The ordinary incidence of leukemia in patients of this age and sex would lead one to expect an occasional case on a chance basis. However, it is not impossible that irradiation of lymphoid aggregates in the hyperplastic thyroid might induce leukemia. Therefore, careful record and tabulation of all similar cases appears desirable.

Two tables; 4 photomicrographs.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

The Turnover Rate of Serum Albumin in the Nephrotic Syndrome as Determined by I^{131}-Labeled Albumin. William H. Blahd, Max Fields, and Ralph Goldman. J. Lab. & Clin. Med. **46:** 747–756, November 1955. (Wadsworth Hospital, VA Center, Los Angeles, Calif.)

Simultaneous albumin turnover and nitrogen balance

studies were performed on 4 patients with the nephrotic syndrome. Balance diets containing both high and low levels of nitrogen were employed. The albumin turnover rate was determined from the disappearance curve of plasma radioactivity following the intravenous injection of tracer amounts of I^{131}-labeled human serum albumin. Simultaneous disappearance curves of urine radioactivity were obtained. Included in the data were the total exchangeable albumin pool and circulating or vascular albumin pool.

The albumin turnover (grams per day) was found to be elevated in 3 of the 4 cases, indicating enhanced albumin production. Total exchangeable albumin pools were markedly diminished; circulating albumin was severely depleted.

The level of dietary nitrogen was closely related to the rate of albumin synthesis. Albumin production was increased when the patients received high protein diets but declined when nitrogen balance became negative following the institution of low-protein diets.

A discussion of methods for calculating exchangeable pools is included in an appendix to this paper.

Five figures; 4 tables.

A Comparison of the Volume of Distribution of Antipyrine, N-Acetyl-4-Amino-Antipyrine, and I^{131}-Labeled 4-Iodo-Antipyrine in Human Beings. Peter J. Talso, Thomas N. Lahr, Norma Spafford, George Ferenzi, and Helen R. O. Jackson. J. Lab. & Clin. Med. **46:** 619–623, October 1955. (Stritch School of Medicine, Loyola University, Chicago, Ill.)

The volume of distribution of antipyrine, N-acetyl-4-amino-antipyrine, and 4-iodoantipyrine was compared in 16 normal individuals. The respective values obtained were 31.6 kg. or 49.7 per cent of the body weight, 31.9 kg. or 50.6 per cent of the body weight, and 31.9 kg. or 50.6 per cent of the body weight. The twenty-four-hour thyroid uptake was measured and found to be 8 per cent of the injected dose. This amount did not appear to interfere with the volume of distribution of 4-iodo-antipyrine during the first eight hours after injection, but could be further reduced by pretreatment with Lugol's solution. Under these circumstances urinary excretion of I^{131} is extremely rapid, 71 per cent of the injected dose being excreted in the first twenty-four hours.

One graph; 1 table.

Clinical Stationary Field Therapy with a Cobalt-60 Unit. Part I. Gilbert H. Fletcher. **Part II.** Gilbert H. Fletcher, Jasper E. Richardson, E. Bailey Moore, Jack M. Morgan, and Arthur Cole. Am. J. Roentgenol. **75:** 91–116; 117–128, January 1956. (G. H. F., M. D. Anderson Hospital, Houston, Texas)

The vital prerequisite in any radiotherapeutic technic is anatomical accuracy. Tumors rarely grow in perfect spheres or cylinders or in simple geometric patterns. In addition, not all parts of a given tumor require the same dose for sterilization. The ability to produce the desired volume distribution, taking into consideration the anatomical location of tumors and their clinical behavior, is made possible by: (1) utilization of anatomical fields, (2) differential skin doses to portals in multiple-field technic, and (3) modification of the field arrangement and of the size of the portals as the treatment progresses, in order to deliver higher doses to more resistant areas.

With these principles in mind, the author discusses the use of cobalt-60 therapy, through fixed fields, of tumors in the head and neck, thoracic cage, pelvis, breast, and genitourinary system. Each of these anatomical areas is discussed, with special attention to the arrangement of portals, based on clinical findings. Allied or additional types of therapy are also briefly considered.

In conclusion, the author points out that, although supervoltage results in greater depth dose, lesser differential bone absorption, lesser integral dose, lesser skin reaction and therefore a somewhat lesser systemic reaction, it is not a panacea and does not do away with the necessity of painstaking clinical management of malignant diseases.

Part II of this paper is concerned with the physical aspects of cobalt-beam therapy. It deals particularly with collimator design and means of shaping the radiation beam.

With short collimator-skin distances, the number of secondary electrons reaching the skin can be reduced by use of a material of intermediate atomic number as an inner lining of the collimator. A significant reduction in skin dose is afforded by electron filters, particularly when large areas are irradiated at short collimator-skin distances. As this distance increases, one is faced with the problem of a larger penumbra, which cannot be used to advantage in stationary field therapy and may cause damage to considerable areas of mucous membrane in the treatment of lesions of the head and neck. In the collimating device at the M. D. Anderson Hospital, from which this report comes, the penumbra problem is met by employment of a light localizer and interchangeable cones.

Shaping the beam of radiation to provide a volume distribution anatomically fitted to the disease to be treated is accomplished with the aid of umbrella diaphragms, wedge filters, and split fields. Isodose measurements obtained with the aid of these devices are reproduced.

Some accessories useful in treatment are also briefly mentioned.

Four roentgenograms; 12 photographs; 13 drawings (field distributions, isodose charts, etc.); 2 tables.

J. H. PURCELL, M.D.
University of Louisville

The Cobalt Bomb in the Treatment of Bladder Tumours. A Preliminary Report. S. M. Busby. Canad. M. A. J. **73:** 872–875, Dec. 1, 1955. (556 Wellington St., London, Ontario)

Between November 1951, when the cobalt-60 beam unit was first put into operation at London, Ontario, and May 1955, 58 cases of primary bladder tumor were treated by this means. The patients ranged in age from thirty-nine to eighty-eight (average 61.6 years). There were 45 men and 13 women. Thirty-three tumors were of the transitional-cell type, 11 papillary, 8 squamous-cell, and 6 anaplastic.

Thirty-four patients were given palliative treatment only, 3,000–4,000 r in three to four weeks. Usually in these cases only two ports (anterior and posterior parallel) were used. Twelve of the patients had reactions and 14 obtained relief of symptoms (bleeding, frequency, dysuria). At the time of the report, 7 were alive, of whom 3 were free of tumor.

Twenty-four patients received radical therapy, 5,000–6,000 r in three to six weeks. Sixteen had reactions. An equal number obtained relief of symptoms.

Thirteen were alive at the time of the report, 5 free of tumor. The trend during the later months of the period covered by this report was toward a higher dosage through four ports over a longer time—up to six and a half weeks. Such a prolonged period, however, sometimes created an economic problem.

Twelve of the 58 cases are presented in some detail. These are divided into three groups of 4 each—patients who did badly and died, those to whom cobalt therapy had something to offer and who did well, and those in whom the results proved a pleasant surprise.

The number of patients and the interval since treatment (less than five years) do not allow any definite conclusions to be drawn. The following important facts should be kept in mind in future similar therapy.

1. Irradiation should not be carried out earlier than three weeks after the bladder is opened to expose the tumor or perform a biopsy.
2. Urinalysis should be done daily, or at least twice weekly.
3. Large necrotic tumors with the usual complication of a grossly infected urine tend to have a poor course during therapy. An attempt should be made to reduce the amount of necrotic tissue on the surface of the tumor and clear up the urine with antibiotics.
4. Cobalt therapy has a definite place in the management of bladder tumors. It should be considered for patients who refuse operation or on whom it is felt unsafe to carry out a long complicated surgical procedure.
5. Multiple bladder tumors which have responded poorly to electrocoagulation have been controlled well by the cobalt bomb.

Rotation Therapy with a Cobalt 60 Unit. I. Physical Aspects of Circumaxial Rotation. Paul M. Pfalzner and W. R. Inch. **II. Transit Dose Measurements as a Means of Correcting Tumour Dose for Non-Water-equivalent Absorbing Media.** Paul M. Pfalzner. Acta radiol. **45:** 51–61; 62–68, January 1956. (P. M. P., Ontario Cancer Foundation, London, Ontario)

Rotation therapy is the logical extension of the cross-fire technic. Its greatest advantage is obtainable with a highly penetrating beam with relatively little side-scatter, such as is furnished by a cobalt-60 unit. Also, with such a beam there is a reduction in differential absorption between fat, bone, and soft tissue which allows phantom measurements to be used with more confidence. The latter, however, does not apply to the thorax with the air-containing lungs.

Circumaxial rotation, as discussed in this paper, involves the use of a stationary teletherapy unit with rotating platform, on which the patient sits erect. The treatment volume is made to lie at the intersection of the axis of the radiation beam and the vertical axis about which the patient rotates.

Calculation of the dose to the tumor area is possible, but is tedious and not entirely reliable, especially at the edge of the beam. Water phantoms were therefore used for dose determination. These were cylindrical vessels of plexiglass with a central plexiglass block containing 304 cylindrical holes. Ionization chambers were placed in the holes to correspond to the treatment pattern and the unused holes were filled with plastic inserts.

Studies on the phantoms demonstrated a rapid falling off of the dose from the central maximum, the relative fall being greater for small fields. The curve of dose distribution was shown to be practically independent of the size of the phantom, but the absolute surface value was lower with thicker phantoms. If less than 360° rotation is employed, the maximum dose shifts away from the center along the bisector of the rotational angle. The absence of change in distribution in phantoms of different size is important, as it permits use of the results without serious error with eccentrically placed tumors and in body areas deviating from a true circle.

Treatment factors are determined by locating the area to be irradiated, following which a paper outline of the body at that level is made. The tumor size and location are indicated on the paper. The field size is then determined. Next, the ratio of dose at the tumor center to air dose is calculated. The daily air dose to allow delivery of the tumor dose in the prescribed time is then estimated. The time of the individual treatment is determined from a slide-rule nomogram. An additional scale on the nomogram is used to find the speed of rotation for an integral number of revolutions during the treatment time.

The constructional details of the rotational equipment are clearly outlined, including the methods of supporting the patient, and the setting-up procedure is given, step by step. The total time required to set up a patient is four to seven minutes.

With the higher-energy radiation provided by a cobalt-60 unit, the absorption in tissue more nearly equals that in water than is the case with conventional roentgen irradiation. Even with a high-energy beam, however, absorption by air-containing lung is considerably less than water-equivalent.

In the second part of this paper, the author describes the use of transit dose measurements to calculate effective water-equivalent chest contours. During irradiation of the chest by the circumaxial technic, the transit dose was obtained for each 10° of rotation, with a dose rate meter at least 70 cm. from the patient in the central axis of the cobalt beam. With these measurements and appropriate calculations, the anatomic contour of the thorax is replaced by a water-equivalent contour. This latter is almost circular, showing the greatest difference from the anatomic outline where the largest volume of lung is traversed by the beam.

With the appropriate depth dose values and isodose charts, the water-equivalent contour allows a more accurate estimate of the dose delivered to the tumor. The reliability of this method was confirmed by the use of small intracavitary ionization chambers attached to an esophageal probe and exposed during the rotation treatment.

Nine illustrations.

J. A. GUNN, M.D.
Grand Rapids, Mich.

Controlled Intratumoral and Intracavitary Radiogold Therapy. H. Oeser, W. Schlungbaum, and H. G. Mehl. Fortschr. a. d. Geb. d. Röntgenstrahlen **83:** 792–802, December 1955. (In German) (Westend-Krankenhaus, Berlin-Charlottenburg 9, Germany)

The use of radioactive colloidal gold introduced either directly into the tumor or into a body cavity has passed the theoretical and experimental stage and is now a practical method of treating malignant disease. Its obvious effectiveness in certain previously untreatable conditions is, however, somewhat counterbalanced by unsolved problems. Of these, the most serious is the calculation of the actual radiation dose at the site of

the malignant process. Other points to be determined include the distribution of the radiogold within the tissue, the most desirable physical state of the colloidal gold, the most favorable injection technic, and the type of tissue best suited for gold injection. Lymphatic transport of the gold from the site of injection is now recognized and considered a desirable event. Hematogenous transport is, on the other hand, quite undesirable because of excessive irradiation to the liver and to the reticuloendothelial system.

To clarify these difficulties the authors suggest that all cases treated with radioactive gold be reported in order that a large series may be compiled. To this end they present 18 cases of their own, all but 2 of which were treated by intratumoral injection.

Colloidal gold with a particulate size of approximately 60 millimicra, stabilized with gelatine, was utilized. Following the injection, the isointensity curves for the entire body were constructed by direct measurement. Curves are reproduced illustrating the distribution of the radiogold in a carcinoma of the tonsils, bone metastasis from a thyroid cancer, and sarcoma of the chest wall. It can be noted that the gold tends to localize well in the injected tissue and that a moderate amount is carried to the liver and the kidneys. One instance is described in which there was an overwhelming dose to the reticuloendothelial system, requiring blood transfusions for control.

The authors claim remarkable clinical responses to the radiogold. It was found possible to administer anywhere from 10,000 to 100,000 rads quite readily and with good localization in the malignant tissue. The radiogold was frequently combined with external deep therapy without untoward results.

Seven figures; 1 table.

WILLIAM F. WANGNER, M.D.
Royal Oak, Mich.

Treatment of Chronic Myeloid Leukemia with Colloidal Radioactive Gold. K. Fellinger, E. Mannheimer, E. E. Reimer, and H. Vetter. Radiol. clin. **25:** 1–11, January 1956. (In German) (II. Medizinischen Universitätsklinik, Wien, Austria)

This report concerns 30 patients with chronic myeloid leukemia, 21 males and 9 females from nineteen to seventy-two years of age, who were followed for at least one year after intravenous injections (average dose, 52 mc) of colloidal Au^{198}. No patient in the terminal phase of the disease was included. The red and white blood cell picture became practically normal, with considerable regression of the size of the liver and spleen. Significant improvement in the clinical state lasted on an average of eight months after the first injection, but only four months after the second. The average survival was 2.4 years.

While treatment with radioactive gold does not definitely lead to a prolongation of survival time as compared with other varieties of therapy, it offers many advantages. Among these are simplicity (one injection) and minimal irradiation reactions and complications. While radiogold is relatively expensive, the patient remains ambulatory during treatment. Since there is practically no excretion of this isotope, there is no problem of radioactive disposal. The treatment is suitable even in those patients who show absolute resistance to chemotherapy and roentgen irradiation.

Nine graphs. CHRISTIAN V. CIMMINO, M.D.
Fredericksburg, Va.

An Experimental Study of Intramammary Injection of Au^{198}. Harold F. Berg and William M. Christophersen. Ann. Surg. **143:** 92–97, January 1956. (University of Louisville, School of Medicine, Louisville, Ky.)

The distribution and effects of radioactive colloidal gold were studied in some 60 dogs following injection into the right superior mammary gland in single and fractional doses. The injected isotope concentrated in the right axillary, cervical, and latissimus dorsi nodes. No appreciable amount was found elsewhere in the body.

Radiation effect was present in lymph nodes receiving as little as 2 mc of Au^{198}. When 10 mc or more was injected, areas of necrosis appeared. Diffuse necrosis of all, or practically all, of the node did not occur until doses of the magnitude of 50 mc were used. The local site of injection did not tolerate these large doses well and sloughs often occurred. Fractionated doses were tolerated somewhat better but did not produce comparable necrosis. As might be expected, the most marked changes were seen in the nodes closest to the injection site.

Since there were no tumors in any of the glands injected, the blocking effect of tumor cells in the nodes and lymph channels could not be evaluated in the present study.

Three diagrams; 3 photomicrographs; 1 autoradiograph. ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Factors Affecting the Rate of Removal of Gelatin-Stabilized Radiogold Colloid from the Blood. I. The Retardation of the Radiogold Disappearance Rate by Gelatin. Irwin M. Murray and Michael Katz. J. Lab. & Clin. Med. **46:** 263–269, August 1955. (I. M. M., 350 Henry St., Brooklyn 17, N. Y.)

In studies performed on rats, the rate of disappearance of gelatin-stabilized radiogold colloid from the circulation following intravenous injection was found to be dependent primarily on and inversely proportional to the amount of gelatin. The disappearance rate of radiogold alone was 50 per cent of the injected dose per minute. One milligram of gelatin per 100 gm. of body weight reduced this rate to 20 per cent of the injected dose per minute. Plasma and plasma fraction IV-4, when injected with gelatin, enhanced the gelatin effect but, when injected alone, did not influence the rate of removal of radiogold.

The possible mechanisms by which gelatin retards the disappearance rate of radiogold are discussed. It is suggested that the decreased rate of clearance of gelatin-stabilized radiogold colloid is due to the formation of a gelatin-gold-plasma complex. The use of blood clearance rates of gelatin-stabilized colloids as a measure of phagocytic activity may not be valid.

Two graphs; 2 tables.

The Radioactive Phosphorus (P^{32}) Uptake Test in Ophthalmology. A Review of the Literature and Analysis of Results in Two Hundred Sixty-Two Cases of Ocular and Adnexal Pathology. Irwin S. Terner, Irving H. Leopold, and Isadore J. Eisenberg. Arch. Ophth. **55:** 52–83, January 1956. (I. S. T., 1601 Spring Garden St., Philadelphia, Penna.)

A series of 262 cases of ocular disease in which P^{32} uptake studies were performed is reported. Two hundred and thirty-three of the patients had intraocular

lesions; in 29 the lesions were extraocular (adnexal). One hundred and twenty-three of these cases were reported previously (Arch. Ophth. **52**: 741, 1954. Abst. in Radiology **65**: 486, 1955) but have now been reviewed in the light of further experience.

Experimental evidence indicates that tumor tissues retain P^{32} over a longer period of time than normal tissue, the differential being expressed as "percentage greater than normal." In this study, readings were performed one hour and twenty-four hours after injection of the isotope. In intraocular lesions the test was considered positive when the uptake was more than 30 per cent greater than normal at one hour, and when an increase beyond the one-hour calculation was evident at twenty-four hours. In lid lesions, the same criteria were applicable, but the test was also interpreted as positive if the one-hour calculation was more than 100 per cent greater than normal, regardless of the twenty-four-hour reading.

Among the 233 intraocular cases, there were 3 false-positive tests in a group of inflammatory lesions and 3 false-negative tests among 30 cases of malignant melanoma. In 4 other cases of intraocular malignant melanoma, in which the clinical diagnosis was obvious and the P^{32} readings had been negative, repeat tests were performed; all of these were positive. In 3 of the latter cases the lesion was posterior to the equator of the globe, and in the fourth, the lesion was anterior to the equator. Of 6 cases of retinoblastoma, there were five false-negative tests.

Among the 29 instances of adnexal lesions there was one false positive test, in a case of basal-cell epithelioma of the eyelid.

On the basis of these studies, and in the light of other experimental work, the following conclusions may be drawn:

1. P^{32} uptake studies are a valuable aid in the differential diagnosis of intraocular disease, especially in the differentiation of serous and solid detachments of the retina, provided the lesion is within reach of the counter tube.

2. Results of P^{32} studies are equivocal in intraocular malignant disease in the posterior segment of the globe, beyond the reach of the presently used counter tube.

3. The test is less accurate in intraocular cases in patients with one eye, in instances of bilateral ocular pathology, and in cases in which previous intraocular surgery has produced an inflammatory reaction.

4. For reasons not yet known, accuracy of the test was found to be decidedly reduced in cases of retinoblastoma.

5. In this study, no correlation could be made between the P^{32} uptake measured *in vivo* as "per cent greater than normal" and the cellular type of the malignant melanoma studied *in vitro* following enucleation.

6. In adnexal lesions the results of the test appear to follow a pattern similar to that with intraocular lesions, except for epitheliomas of the lids.

7. P^{32} testing prior to surgery in certain adnexal lesions occasionally offers the surgeon an advantage otherwise attainable only by biopsy. In lid lesions the test is less advantageous, as most such lesions are easily accessible to biopsy or surgical excision without risk of tumor spread.

8. The validity of the P^{32} uptake test depends upon (*a*) the ability of malignant tissue to concentrate the isotope, (*b*) the capacity of malignant tumor tissue to retain P^{32} over a period of time, and (*c*) the faculty of normal tissues to excrete their initial concentration of P^{32} rapidly.

An extensive review of the literature is included.

Twenty-five illustrations; 4 tables.

The Uptake of Radioactive Phosphorus in Normal Breast and Breast Tumors. N. N. Das Gupta, K. L. Bhattacharya, R. Dutt Choudhuri, A. Bose, and P. K. De. Acta radiol. **45**: 69–80, January 1956. (Chittaranjan Cancer Hospital, Calcutta, India)

Radioactive phosphorus was administered to 48 patients with palpable breast tumors, and the superficial beta activity over the tumor and over the corresponding site in the normal breast was measured. The P^{32} was administered intravenously, the dose being 0.01 microcurie per gram of body weight. The measurements were made with a thin-wall Geiger-Müller tube (wall thickness 35 mg./cm.^{2}) in contact with the skin and were repeated at two, six, ten, twenty-four, thirty, thirty-six, and forty-eight hours after the injection. The average surface counting rate was considered to be the most significant as an indicator of malignancy.

Of the 48 tumors studied, 20 were histologically malignant, and in 17 of these the count was more than 130 per cent of that in the normal breast tissue. Of the 28 benign tumors, 23 gave counts less than 130 per cent, and a large proportion were within 110 per cent of the normal.

If, in view of these results, a counting rate over the tumor equal to or greater than 130 per cent of that over the normal breast be regarded as suggestive of malignancy, then the diagnosis based on tracer measurements agreed with the histologic findings in 40 out of 48 cases.

Three graphs; 1 drawing; 2 tables.

J. P. CHAMPION, M.D.
Grand Rapids, Mich.

Bone Metabolism. II. Toxicity and Metabolism of Radioactive Strontium (Sr^{90}) in Rats. Robert D. Ray, Duncan M. Thomson, Norvelle K. Wolff, and Duane La Violette. J. Bone & Joint Surg. **38-A**: 160–174, January 1956. (University of Washington School of Medicine, Seattle, Wash.)

Having previously compared the metabolism of strontium 90 in living and dead bone (J. Bone & Joint Surg. **37-A**: 143, 1955. Abst. in Radiology **65**: 831, 1955), the authors here report on the toxicity of the isotope and review the histological and physiological changes induced by it.

By giving intraperitoneal injections to 11 rats, it was found that 2.5 to 3.0 microcuries per gram of body weight was sufficient to cause death in half of the number in fifty to sixty days. Most of the animals lost weight and exhibited an apparent tendency toward respiratory tract hemorrhage. In addition, the rats that died early showed degenerative changes in the renal tubules. Bone studies of the tibias of the surviving animals revealed fibrosis of the marrow, metaphyseal hemorrhages, absence of vascular channels with aseptic necrosis of trabecular bone, and depression of myeloid elements. These alterations were presumed to be due to beta radiation from the isotope.

The Sr^{90} appeared to be metabolized in a manner similar to calcium. There were rapid absorption from the peritoneal cavity into the blood stream and rapid skeletal uptake. Mobilization from the skeleton was very gradual, probably due partially to radiation damage to the cellular elements of the bone.

Most of the injected isotope was excreted in the urine, but there was also significant excretion by way of the feces.

Potential industrial and clinical uses of Sr^{90} appear to make these investigations very worthwhile. Similar studies over longer periods are promised for later papers.

Four photomicrographs; 6 charts; 4 tables.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Tantalum 182 Wire Gamma-Ray Applicators for Use in Ophthalmology. N. G. Trott and B. M. Wheatley. Brit. J. Radiol. **29:** 13–14, January 1956. (Institute of Cancer Research, Royal Cancer Hospital, London S. W. 3, England)

Tantalum 182 (half-life 111 days; mean gamma-ray energy 1.13 MEV; k factor 6.13 r/hr./mc at 1 cm.), in the form of wire enclosed in Polythene tubing and formed into rings of various diameters, has been found useful in certain lesions of the eye. If the activity of the wire is 1.0 mg. radium equivalent per centimeter, the dose-rate for a 1 cm. ring at a central point 0.5 cm. from the plane of the ring is 52.2 r/hr.

Methods are outlined in this paper for treating malignant melanoma on the under surface of the upper eyelid and retinoblastoma. Dose computations and isodose curves are given for a typical application.

One figure. DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

An Automatic Controlled Pattern Cesium 137 Teletherapy Machine. Marshall Brucer. Am. J. Roentgenol. **75:** 49–55, January 1956. (P. O. Box 117, Oak Ridge, Tenn.)

This is a preliminary report on the experimental teletherapy machine constructed to accept the first multikilocurie source of cesium 137 at the Medical Division of ORINS. The machine was completed in 1954 and loaded with a 1,540 curie source of cesium 137. The design of the unit and its mechanism of operation are exceedingly complex, and readers are referred to the original article for details.

The machine will be available for the treatment of patients under the direction of the ORINS Teletherapy Evaluation Program, but its primary purpose is not routine therapy. It was designed to study dosimetry in various patterns of rotation, to determine the integral dose as a function of rotational pattern and energy, and to achieve comparative studies with iridium, europium, cerium, and other isotopes.

The advantages and disadvantages of the use of cesium 137 in teletherapy are presented. The most important of these are listed as follows:

Advantages

1. Supervoltage (0.661 MEV)
2. Differential attenuation in high and low Z materials
3. Long half-life
4. Large scale production
5. Waste product of all reactors

Disadvantages

1. Low specific activity
2. Low gamma intensity
3. Chemical preparation of a powdered salt
4. Not available until 1957

Most of the hectocurie cobalt-60 machines now in use are capable of receiving cesium 137 sources for straightforward routine therapy. No special problems are foreseen in the use of the isotope beyond minor adjustments in dosimetry. The purpose of this exceedingly complex device is to study therapeutic procedures unhampered by the bias of mechanical restrictions as in conventional simple rotational patterns available with either a moving chair or a moving beam.

Three photographs; 3 drawings; 2 graphs; 2 tables.

J. T. LING, M.D.
University of Louisville

The Study of Erythropoiesis Using Tracer Quantities of Radioactive Iron. T. H. Bothwell, Sheila Callender, Barbara Mallett, and L. J. Witts. Brit. J. Haematol. **2:** 1–16, January 1956. (Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, England)

Plasma iron, while constituting only about 0.1 per cent of the total body iron, is an extremely important fraction, since it represents the sole means of transport of iron from one part of the body to another. The authors labeled the plasma iron with Fe^{59} and made tracer studies in 64 patients, most of whom were suffering from blood disorders of various types.

The quantity of iron passing through the plasma per hour was calculated for each subject, and in most an estimate of red-cell utilization was made. Difficulties were encountered both in technic and in interpretation of results. Diurnal variations occurred in the rate of turnover of plasma iron, and the disappearance of radioiron from the plasma could not always be approximated by a single exponential function. Further difficulties arose in determining the point at which the incorporation into red cells of radioiron initially taken up by the marrow is complete, which end-point should be known in deriving the daily red-cell iron turnover from the plasma iron turnover. The results are not considered, therefore, to have provided a reliable quantitative measure of the rate of blood formation.

The authors believe, nevertheless, that the radioiron tracer technic has considerable qualitative value. They were able to recognize definite alterations in the pattern of erythropoiesis. Clearance of the injected iron was rapid in iron-deficiency anemias, hemolytic anemias, and polycythemia vera, but slow in hypoplastic marrow states. The utilization of the injected radioiron was complete or almost complete in iron-deficiency anemias and in polycythemia vera but reduced in hemolytic anemias and much decreased in hypoplastic anemias. In addition, the method proved useful in differentiating polycythemia vera from cases of "relative" polycythemia characterized by increase in hemoglobin, red-cell count, and hematocrit, without increase in the red-cell mass.

Two figures; 1 table. ARTHUR S. TUCKER, M.D.
Western Reserve University

Red Cell Stroma and Hemoglobin Metabolism in Anemic Dogs. Regeneration of Red Cell Proteins Labeled with C^{14} Lysine. G. H. Tishkoff, C. L. Yuile, F. S. Robscheit-Robbins, and G. H. Whipple. J. Exper. Med. **102:** 713–723, Dec. 1, 1955. (Department of Pathology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.)

Previous studies on the life span of red blood cells, into which C^{14}-labeled amino acids had been incor-

porated, were concerned with whole cells and no attempt was made to distinguish the activity of hemoglobin from other red cell constituents. In the investigation described here the C^{14} activity of erythrocyte hemoglobin was compared with that in stromal protein throughout the life cycle of the red blood cell in 5 dogs. *Dl*-Lysine-ϵ-C^{14} was fed to 3 animals with anemia produced by repeated bleeding, to 1 with anemia and hypoproteinemia, and to 1 with anemia due to phenylhydrazine. During the period of *active regeneration from anemia*, red cell hemoglobin and stroma protein exhibit some degree of independence with regard to incorporation of C^{14}.

Stroma proteins are produced and a maximum concentration of the C^{14} label appears two to three days earlier than with hemoglobin, *i.e.*, stroma building precedes hemoglobin construction. The concentration of isotope in stroma protein may exceed its concentration in hemoglobin during regeneration following anemia due to blood loss. Diets favorable for hemoglobin regeneration may force the hemoglobin isotope concentration above that of the stroma protein.

In hemolytic anemias great reserves of red cell building material are stored in the body. These stores may modify the curves of isotope concentration in red cells during the recovery periods.

When finally formed, mature red cells show little or no evidence of participation in general body protein metabolism during their life in the circulation.

Four graphs; 3 tables.

Demonstration of Stimulation of Erythropoiesis by Plasma from Anemic Rats Using Fe^{59}. Louis F. Plzak, Walter Fried, Leon O. Jacobson, and William F. Bethard. J. Lab. & Clin. Med. **46:** 671–678, November 1955. (Argonne Cancer Research Hospital, Chicago, Ill.)

Plasma from rats made anemic by bleeding is shown to contain a humoral substance that stimulates erythropoiesis in normal rats. The activity of this substance was demonstrated by an increase in the rate of incorporation of Fe^{59} into red blood cells following infusion of anemic plasma. Plasma equal in amount to about one-half of the animal's blood volume is required to cause this stimulation. Best results were obtained with three doses of 2 ml. each. The Fe^{59} solution must be injected within a few hours following the final infusion of anemic plasma, and blood samples should be obtained twelve hours afterward.

Four graphs; 5 tables.

The Use of ^{86}Rubidium as a Label for Red Cells. G. R. Tudhope and G. M. Wilson. Brit. J. Haematol. **2:** 75–79, January 1956. (Department of Pharmacology and Therapeutics, University of Sheffield, Sheffield, England)

The authors compare the usefulness of various radioactive isotopes in the estimation of total red-cell volume. Rb^{86} has been found to have a distribution between red cells and plasma similar to that of P^{32}. In their work they utilized $Rb^{86}Cl$, $Rb^{86}{}_2CO_3$, or $NaHP^{32}O_4$ obtained from Harwell, dissolved in isotonic saline.

In 6 *in vitro* experiments the uptake of Rb^{86} and P^{32} by red cells and the subsequent leak of the isotopes from the cells were compared simultaneously under identical conditions, using different aliquots of the same sample of blood. In 4 additional experiments Rb^{86} was used alone. After three hours incubation approximately one-third of the rubidium had entered the cells. The amount of phosphorus which entered was higher, but not significantly so. On the other hand, the leakage of P^{32} was greater than that of Rb^{86} at one, two, and three hours by differences which were highly significant (in each comparison $P < 0.01$).

In vivo studies were made on 3 patients injected with Rb^{86} and 2 with P^{32}. The half-times of disappearance of the Rb^{86} from the red cells were thirty-six, forty, and fifty-four hours; those for P^{32} were twenty-four hours.

Cr^{51} is mentioned as being a much more efficient label for red cells than either Rb^{86} or P^{32}, but it has the disadvantage of requiring a scintillation counter for measurement. Rb^{86} is considered to offer some advantages over P^{32} because of greater stability, as evidenced in both the authors' *in vitro* and *in vivo* experiments. In addition, Rb^{86} has gamma- as well as beta radiation, and mention is made of the possibility of following the distribution of the Rb^{86} label within the body by the use of an external counter.

One figure; 1 table. ARTHUR S. TUCKER, M.D.
Western Reserve University

A Method Employing Radioactive Chromium for Assaying the Viability of Human Erythrocytes Returned to the Circulation After Refrigerated Storage. John G. Gibson, II, and Walter A. Scheitlin. J. Lab. & Clin. Med. **46:** 679–688, November 1955. (Harvard Medical School, Boston, Mass.)

A method for determining the post-infusion survival of stored human erythrocytes employing Cr^{51} as a tag is described. A closed system for tagging and administration of whole blood eliminates risks of contamination involved in cell washing. The initial radiation received by subjects in a typical experiment is approximately one-fifth of the accepted tolerance dose.

One graph; 1 table.

Survival of Radiochromate-Labeled Platelets in Rabbits. Mary C. Morgan, Richard P. Keating, and Edward H. Reisner, Jr. J. Lab. & Clin. Med. **46:** 521–529, October 1955. (St. Luke's Hospital, New York, N. Y.)

A method for labeling rabbit platelets with Cr^{51} as sodium chromate is presented, and the survival of the labeled platelets is described, both in normal rabbits and in those in which thrombocytopenia was induced by the injection of human serum. In the latter animals, a fall in red cell radioactivity was observed, which the authors ascribe to the hemolytic effect of injected heterologous serum; the increase in plasma radioactivity in these animals is a natural result of the release of radiochromate from destroyed platelets and red cells. That the spleen is not responsible for the thrombocytopenia resulting from heterologous serum injection is indicated by (1) rapid decrease of platelets and platelet radioactivity in splenectomized animals, and (2) similar concentrations of radioactivity in the spleens of animals injected with heterologous and homologous serum. The concentration of radioactivity in the spleen in animals injected with the labeled platelets suggests that this organ was an important site of destruction for tagged platelets.

It was found that rabbit platelets labeled *in vitro* survived on re-injection and that a significant degree of platelet radioactivity was recovered from the circulation for three days. Evidence that the labeled platelets retain their function is presented. It is concluded that

radiochromate tagging affords a tool of value in the study of the life span of platelets in the rabbit.

Two graphs; 5 tables.

The Plasma Clearance and Urinary Excretion of Parenterally Administered ^{58}Co B_{12}. D. L. Mollin, W. R. Pitney, S. J. Baker, and J. E. Bradley. Blood 11: 31–43, January 1956. (Department of Pathology, Postgraduate Medical School of London, London, England)

Vitamin B_{12} labeled with the short lived isotope $^{58}Co^{14}$($^{58}CoB_{12}$), in a dose of 1.5μg., was given intravenously to subjects with normal serum B_{12} concentrations, to patients with vitamin B_{12} deficiency, and to patients with chronic myelocytic leukemia. The rate of plasma clearance of radioactivity after this dose was slowest in patients with chronic myelocytic leukemia and patients with pernicious anemia in severe relapse.

In patients with vitamin B_{12} deficiency, serum B_{12} concentrations were estimated microbiologically at frequent intervals after the injection. There was a good correlation between the results obtained by microbiological assay and as calculated from plasma radioactivity.

Significant differences were not observed between the urinary excretion of radioactivity by normal subjects and patients with B_{12} deficiency.

Four graphs; 6 tables.

The Use of C^{14}-Labeled Acetate to Study Cholesterol Metabolism in Man. R. Gordon Gould, George V. LeRoy, George T. Okita, Jon J. Kabara, Patricia Keegan, and Delbert M. Bergenstal. J. Lab. & Clin. Med. **46:** 372–384, September 1955. (R. G. J., Los Alamos Scientific Laboratory, Los Alamos, N. Mex.)

The studies described in this report were undertaken, first, to ascertain the rate at which cholesterol-C^{14} appeared in the plasma after the administration of carbon-14-labeled acetate to man and, second, to determine the relationship between the dose of acetate and the specific activity of the labeled cholesterol. The studies, performed in 34 patients, were carried out using 100 to 200 μc of carboxyl-labeled sodium acetate (1-C^{14} acetate), given orally or intravenously. The changes occurring within the first twenty-four hours are particularly described.

The rate of hepatic cholesterol synthesis can be roughly estimated from the maximum plasma-free cholesterol specific activity value for normocholesterolemic patients, with a correction required in the case of hypo- or hypercholesterolemic patients. The percentage of the dose of C^{14}-acetate incorporated into the total liver-blood cholesterol may be calculated and is also an index of hepatic cholesterol synthesis.

The rate of interchange of free cholesterol between liver and plasma was found to be at least 0.87 gm. per hour in each direction.

In man, the cholesterol-C^{14} in the red cells comes into equilibrium with plasma-free cholesterol-C^{14} within eight to twelve hours. The plasma esterified cholesterol is derived from the free fraction at a slower rate, so that equilibrium is seldom achieved before twenty-four to forty-eight hours following the administration of the tracer dose.

The fraction of the carboxyl-labeled acetate that is utilized for cholesterol synthesis was found to be approximately 1.04 per cent in normal subjects, 0.23 for patients with myxedema, 4.0 for cancer patients, and 4.75 for patients treated with cortisone. It is apparent that the metabolic state of the subject produces marked variations in the rate of hepatic cholesterol synthesis.

Three graphs; 6 tables.

Determination of Carbon^{14}-Labeled Acetate Utilization by Tubercle Bacilli. Betty Jo Tricou, Dieter Koch-Weser, Robert H. Ebert, and Robert A. Barber. J. Lab. & Clin. Med. **46:** 917–923, December 1955. (Department of Medicine, University of Chicago, Chicago, Ill.)

A method for study of acetate utilization by tubercle bacilli is presented. It consists of adding C^{14} methyl-labeled acetate to the microorganisms in Conway units and determining the C^{14} uptake and the conversion to $C^{14}O_2$ by the bacilli.

Study of the acetate utilization during different phases of growth and after submitting the cultures to varying temperatures indicates that this method permits evaluation of the metabolic activity of a small number of bacteria at any age and under different metabolic conditions.

Parallel determinations of tri-phenyl-tetrazolium chloride reduction suggest that this is independent of O_2 availability, while the acetate utilization seems to depend upon O_2 available to each microorganism.

Five graphs; 1 diagram; 1 table.

Absorption of Radioactive Vitamin B-12 in the Syndrome of Megaloblastic Anemia Associated with Intestinal Stricture or Anastomosis. James A. Halsted, Peter M. Lewis, and Marvin Gasster. Am. J. Med. **20:** 42–52, January 1956. (J. A. H., VA Hospital, Syracuse, N. Y.)

The syndrome of megaloblastic anemia associated with intestinal stasis is characterized by a clinical appearance similar to that of pernicious anemia. The bone marrow and peripheral blood pictures are much the same, and in both diseases there may be seen glossitis and subacute combined degeneration of the spinal cord.

Megaloblastic anemia associated with intestinal stricture or anastomosis is evidently the result of vitamin B_{12} deficiency, and responds to vitamin B_{12} therapy. The mechanism is believed to be that of bacterial interference with normal utilization of vitamin B_{12}, with secondary adverse effect upon hematopoiesis. Small bowel stricture, anastomosis, or blind loop causes intestinal stasis and favors the development of abnormally luxuriant bacterial growth in the stagnant loop or segment. The bacteria absorb vitamin B_{12} and thus deny it to the body.

To test this concept, 2 patients were given vitamin B_{12} labeled with radioactive cobalt, orally. Measurements of the amount of radioactivity in the stools thereafter gave an index of the amount of vitamin B_{12} absorption in the intestine.

Results seemed to support the theory that the presence of stricture or anastomosis was associated with impaired vitamin B_{12} absorption. Treatment with Aureomycin or Achromycin was followed by return of absorption to normal. Administration of neomycin, however, failed to produce such an effect, indicating that bacterial competition may not be the whole answer.

Three figures; 2 tables. DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

RADIATION EFFECTS

Radiation Hazards to Nonradiologists Participating in X-Ray Examinations. Max Ritvo, Giulio J. D'Angio, and Ivan E. Rhodes. J.A.M.A. **160:** 4–10, Jan. 7, 1956. (M. R., 416 Marlborough St., Boston, Mass.)

Serious and even fatal injuries from overexposure to x-radiation continue to occur, especially among physicians untrained in radiology, who, nevertheless, perform roentgen diagnostic procedures. Carelessness, indifference, and ignorance are chiefly responsible. The three tissues predominantly affected are the skin, gonads, and hematopoietic centers. Skin damage ranges from erythema to ulceration and even to carcinoma of a highly malignant type. The blood picture may range from aplasia of the bone marrow or leukopenia to leukemia. Sterility is perhaps the extreme effect of gonadal overexposure. However, it is well known that first generation offspring of radiologists show a statistically significant higher incidence of congenital abnormalities and following generations should show an even higher incidence as predicted on the basis of animal experiments.

The authors studied the amount of exposure received by non-radiological personnel who participate repeatedly in the performance of x-ray examinations at the Boston City Hospital. Pocket dosimeters with a range up to 200 milliroentgens, with a margin of error up to 10 per cent, as well as Victoreen ionization chambers were used in this survey. Both dosimeters were calibrated against a standard source of gamma radiation (radium). Most of the measurements were made under everyday working conditions with the dosimeters fastened to the dorsum of the hands, abdomen, pelvic areas, etc. The x-ray machines were the usual standard American makes with an inherent filtration of 0.5 mm. Al, with 1 to 3 mm. of additional Al.

During cystourethrography the simple precaution of removing the hands from the direct beam reduced the exposure markedly. In addition, the use of the smallest practicable cone and added filtration (1.5 mm. Al) further reduced the dose to the urologist.

In angiocardiography the use of a cone just sufficient to encompass the film frame was shown to decrease the exposure markedly and incidentally to improve the quality of the resulting roentgenograms.

In femoral arteriography and lumbar aortography a vertical, flexible leaded-rubber sheet (equivalent to 0.5 mm. Pb) was interposed between the operator's hands and the x-ray tube just prior to making the injection and exposing the films. This lowered the dose appreciably. In cerebral angiography, a right-angle Masonite shield with 1 mm. sheet lead was used to protect the surgeon's hands. With this shield the average dose was 50 mr to the right hand and 8 mr to the left; without it, the exposure was increased some twenty times, well above the currently accepted safe limits of 300 mr per week.

During cardiac catheterization the dose to the surgeon is not of great moment according to present standards. However, with the usual factors, five minutes of fluoroscopy gave the patient an entrance dose of 60 r and an exit dose of 0.675 r. With such exposure, repeat examinations of the chest and great vessels, particularly in infants and children, should be undertaken with caution.

During bronchography, myelography, and hip-nailing, the prime protection is distance from the emergent beam. As in all procedures, distance, particularly in relation to the secondary scattering from the patient and from the "Bucky slot," is important.

The proper installation of safely constructed equipment in rooms where the walls and ceiling are far enough away from the primary beam to avoid scattering to the personnel proceeding with the examination is fundamental. In addition, it is the responsibility of the radiologist to be aware of the hazards involved in order to protect himself, his staff, and the non-radiologists participating in the examinations.

Two illustrations. SAUL SCHEFF, M.D.
Boston, Mass.

Late Follow-Up Studies After Internal Deposition of Radioactive Materials. William B. Looney and Martin Colodzin. J.A.M.A. **160:** 1–3, Jan. 7, 1956. (W. B. L., Massachusetts General Boston, Mass.)

This paper presents, in relatively brief form, some of the observations on the late effects of ingested and injected radium and thorium considered at greater length in a three-part paper in the *Journal of Bone & Joint Surgery* (**37-A:** 1169, 1955, and **38-A:** 175 and 392, 1956. Abst. in Radiology **67:** 642, 1956).

The radium studies were based on 78 patients, including 28 former luminous dial painters and 50 persons who had taken radium medically. Radium is deposited in the skeleton in small areas of high focal concentration. Malignant tumors and roentgenographic changes and symptoms resulting from increased fragility of the bones may occur many years after deposition. Thirteen malignant bone tumors were found in the series studied.

Thorium effects were observed in 35 patients who had received Thorotrast for diagnostic studies on an average of fifteen years earlier. Although minute amounts of thorium are found throughout the body, the bulk is stored in the reticuloendothelial system—liver, spleen, and bone marrow—with a lesser degree in the lungs and adrenals. With increasing time after administration, the aggregates of thorium become larger, as seen roentgenographically in the liver and spleen and histopathologically in other organs of the body.

The bulk of the ionizing radiation liberated by thorium and its decay products is in the form of the very short-range alpha particles. Because of this short range and the large Thorotrast accumulations, the authors feel that destruction of tissue is precluded by autoabsorption. Exceptions to this lack of tissue destruction occur at the sites of injection in the neck and arm, where marked induration occurs, and in the spleen, which shows progressive fibrosis, so that in extreme cases only a remnant of the organ remains. A small number of primary hepatic tumors, leukemias, and other hematological disorders following Thorotrast administration have been reported by others, while one of the patients in the authors' series died of a malignant process involving the liver and spleen. There are minor radiographic changes in the endosteal surfaces of the long bones of the extremities where aggregates of Thorotrast are deposited. These consist of irregularity of the endosteum and thickening of the mid-portion of the shaft and of the trabeculae.

SAUL SCHEFF, M.D.
Boston, Mass.

Obstruction of the Ileum after Irradiation for Cancer of the Cervix. William P. Smith and Roy E. Swenson. Am. J. Surg. 91: 121–125, January 1956. (W. P. S., 9 Buttles Ave., Columbus 8, Ohio)

The authors report a case to call attention to the fact that diarrhea, hemorrhage, or obstruction occurring in a patient previously irradiated for carcinoma of the cervix may be due to effects of the radiation rather than to persistence, recurrence, or metastasis of the primary lesion.

A 56-year-old Negro woman was seen because of a dark vaginal discharge of three to four months duration. Cervical and uterine curettings revealed squamous-cell carcinoma of the cervix, Grade III, associated with severe inflammatory reaction. Radium needles were inserted into the cervix for 2,684 mg. hr., and a tube was placed in the fundus to give 3,550 mg. hr. radiation.

Follow-up examination seventy days after operation revealed appreciable shrinkage of the cervix. The patient had by then begun to complain of constipation. One hundred and ten days after surgery she was readmitted because of severe pain in the epigastrium for twenty-four hours, with associated nausea and vomiting. Roentgenograms suggested partial small bowel obstruction. Abdominal exploration on the thirteenth hospital day showed numerous dense adhesions between the loops of the small bowel and the omentum, and a fusiform rubbery mass in the terminal ileum approximately 20 cm. from the ileocecal junction, densely adherent to the uterine fundus, the pelvic floor, and adjacent loops of terminal ileum. The mass was with some difficulty freed and resected, proving to be a segment of ileum 19 cm. long. No grossly demonstrable metastatic lesions were encountered.

Microscopic examination of the specimen showed the mucosa of the small bowel extensively ulcerated and denuded, and the underlying submucosa markedly thickened and edematous. The arterioles were thickened and sclerotic. The pathologic diagnosis was: (1) marked arteriosclerosis, probably radiation effect; (2) thrombophlebitis; (3) infarction, focal; (4) intestinal obstruction, postirradiation.

The postoperative course was without great significance. After five months "passage of mucus had ceased and bowel movements were normal, but slight distention appeared postprandially."

[It should be pointed out that the summary of this case report is inconsistent with the facts as given. The authors state: "A case of carcinoma of the cervix has been presented which required surgical intervention for intestinal obstruction (ileum) seventy-one days after irradiation for the cervical malignancy." By their own account it was seventy-one days from the time the patient was first seen until she first complained of constipation. The interval between the insertion of radium and the subsequent surgical intervention was one hundred ten days. Even so, this is an unusually short interval for radiation fibrosis to develop to the point of obstruction. Also it is surprising that the surgical specimen showed no evidence of carcinoma after this period of time. The illustrations of the specimen, both gross and histologic, are compatible with other diagnoses, *e.g.*, regional enteritis. No diagnostic barium studies were made.

A factor in the patient's condition which the authors do not explain is a hypertension of 210/110, which did not respond, during the first hospitalization, "to rest or sedation or to several of the most recent blood pressure depressants." Among the diagnoses on her second admission were "severe hypertensive cardiovascular disease with impending cerebral disaster" and "early cardiac decompensation." The blood pressure then was 196/130. Yet following the use of Levin tube decompression of the bowel and Wangensteen suction the blood pressure "slowly declined, and on the eighth hospital day it ranged from 136/78 to 156/70. Could the hypertension in some manner have been related to the partial obstruction in the ileum, inasmuch as it appears that relief was obtained immediately following decompression?—A. S. T.]

One roentgenogram; 1 photograph; 1 photomicrograph.

ARTHUR S. TUCKER, M.D.
Western Reserve University

Intestinal Injury Due to Intravaginal X-Ray Irradiation. Erich Buchmann. Strahlentherapie 99: 39–46, January 1956. (In German) (Röntgen- und Geschwulstinstitut des Rudolph Virchow–Krankenhauses, Berlin, Germany)

Intravaginal x-ray irradiation has been employed in combination with intrauterine radium insertion and external x-ray therapy for twenty-five years, but only an occasional paper on its dangers and complications has appeared.

The author reports on three forms of intestinal damage caused by intravaginal irradiation, which are likely to occur more frequently than the damage to the urinary bladder and the rectum which is so often mentioned in the literature. He particularly stresses the importance of exact focusing of the intravaginal cone.

The first case was that of a forty-six-year-old female, who had a perforation of the ileum due to an irradiation ulcer, with ensuing fatal peritonitis.

The second case was one of irradiation stricture of the sigmoid with incomplete ileus, in a woman of fifty-two years.

The third patient was a fifty-seven-year-old female who, eight months after combined therapy, complained of ileus-like symptoms which were relieved by a colostomy. On operation a stenosis of the rectum due to irradiation infiltration of the small pelvis was found. Two years later the rectal stenosis had regressed to such a degree that the colostomy could be closed. The patient was then free of complaints for two more years, at the end of which an acute ileus suddenly developed. Again, there was no evidence of cancer on operation and microscopic examination. A marked constriction of the rectum was present due to scar formation and fibrosis, leading to stenosis.

This last case demonstrates both possible forms of stenosis. The first stenotic reaction occurred six to eight months after irradiation and regressed after colostomy. The second stenosis was observed as a late reaction five years after therapy.

All three patients had, in common, acute inflammatory intestinal reactions during the irradiation, which always regressed. After each treatment they complained of enteritis with extensive pain, so that the procedure had to be interrupted or discontinued completely. Most probably there was an erythema of the intestinal mucosa with hyperemia, edema, and spasms.

The author discusses the dangers of intravaginal therapy and recommends protraction or complete discontinuance of this procedure in patients with evi-

dence of irritation of the intestinal tract. The reduction of the intravaginal dose can be offset by saturation by radium insertion combined with external rotation therapy.

Five roentgenograms; 4 photographs and photomicrographs.

HERBERT C. POLLACK, M.D.
Chicago, Ill.

Skeletal Lesions Following Internally Administered Radium. Richard H. Marshak, Robert A. Newburger, and Joan Eliasoph. J.A.M.A. **160:** 41–44, Jan. 7, 1956. (J. E., 112 Hoyt St., Stamford, Conn.)

The authors report the late results of internally administered radium as observed in a man of fifty-eight who had received intravenous injections of radium salts and a "small quantity of radium water" forty years earlier for arthritis. Roentgen studies of the skeleton disclosed involvement of the metaphyseal regions of the long bones at the knees, ankles, and wrists by extensive areas of altered architectural structure consisting of a distorted and coarsened trabecular pattern and irregular focal areas of sclerosis. In the lower ends of the tibias, these changes were interspersed with large discrete areas of rarefaction. The joint spaces at the hips, knees, wrists, and ankles were considerably narrowed, and the articular margins of the bones involved were irregular. Bone production was noted at the weight-bearing joints particularly. The shoulder joints were narrowed and the humeral heads deformed. The carpus was small bilaterally and the carpal bones irregular in configuration. There was marked osteoporosis about the wrists, shoulders, pelvis, and hips. The skull, other than for slight sclerosis at the base of the middle fossa and diffuse demineralization, showed no further abnormalities. All but two of the teeth were missing, and these had erosions of the dentine and enamel. The mandible was atrophic, with thinning and coarsening of the trabecular pattern. The findings appeared to be due to a combination of radiation osteitis, rheumatoid arthritis, and secondary hypertrophic osteoarthritis.

A Geiger-Müller counter showed increased radioactivity over the knees, ankles, wrists and temporomandibular joints. Determinations on air expired by the patient led to an estimate of retention of 0.2 mcg of radium in the patient's body.

Six roentgenograms.

SAUL SCHEFF, M.D.
Boston, Mass.

Occurrence of Femoral Neck Fractures Following Gynecological Deep X-Ray Therapy. Günther Baerwolff and Paul Otto Buchhorn. Strahlentherapie **99:** 72–78, January 1956. (In German) (Röntgen- und Strahleninstitut des Rudolph Virchow-Krankenhauses, Berlin, Germany)

In the last few years there have appeared numerous reports of spontaneous fractures of the femoral neck following deep x-ray therapy for gynecologic cancer.

The customary technic (Kepp) involved the use of two abdominal fields, two gluteal fields and one vulvoperineal field, with 10 × 15 cm. portals In very obese patients two lateral fields were added to obtain the required depth dose. When spontaneous femoral neck fractures occurred, these lateral fields, which were directly centered over the greater trochanters, were thought to be responsible, but although their use was discontinued, femoral neck fractures were still frequently observed.

With the use of the abdominal and gluteal fields described above, spontaneous femoral neck fractures are to be expected in 1 to 2 per cent of patients treated. The dose in the femoral neck under these conditions is 65 per cent of the dose to the parametrium. When, however, the size of the portals is reduced to 8 × 10 cm., the dose received by the femoral neck is decreased to 20–27 per cent.

The authors' investigations, consisting in photographic recording of fields and dose measurements at the neck of the femur in cadavers, shows that the 8 × 10 cm. fields yield a homogeneous irradiation of the true pelvis with sufficient protection of the femoral neck to prevent spontaneous fractures.

Four roentgenograms; 2 tables.

HERBERT C. POLLACK, M.D.
Chicago, Ill.

Development of Liver Carcinoma in Thorotrast Deposits. Theodor Matthes. Strahlentherapie **99:** 94–106, January 1956. (In German) (Geschwulstklinik der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Buch, Germany)

Various types of tissue damage have been encountered many years after intravenous injections of Thorotrast. Beside the formation of fibrous-sclerotic granulomas at the injection site, remote reactions have been observed, with storage of the radioactive material in the reticuloendothelial system of liver, spleen, and bone marrow. Two of these late sequelae are of special importance: (1) injury of the hematopoietic system followed by a usually fatal panmyelopathy; (2) development of malignant tumors in an area of concentrated Thorotrast deposit.

One of the reasons for publication of this paper is the increasing medical use of radioactive isotopes and the possibility of the subsequent development of cancer.

The author presents 2 cases in which primary liver carcinoma developed in areas of concentrated Thorotrast deposits, about twenty years after intravenous injection of the contrast medium.

The first patient was a 53-year-old white female who, twenty years before, had received an intravenous injection of 80 c.c. of Thorotrast for hepatolienography. X-ray examination of the right elbow joint revealed a large calcific shadow, the size of a cherry. Opaque lines, extending from this shadow, represented contrast deposits in the wall of the cephalic vein, which had been used for the injection. X-ray examination of the abdomen showed Thorotrast in the spleen, liver, and regional lymph nodes. On operation, a liver carcinoma was found, surrounded by deposits of the medium. Lymph-node metastases were present in the left thigh and left axilla.

The second patient was a 52-year-old white woman who had also undergone hepatolienography with Thorotrast (60 to 70 c.c.). A small, hard tumor had been removed from a slightly enlarged liver about eighteen years later. This tumor weighing 20 gm. contained 2 gm. of thorium, equal to about 14 per cent of the previously injected amount. The present examination revealed a metastatic tumor in the left neck, shown microscopically to be an adenocarcinoma, surrounded by Thorotrast deposits. At autopsy a large liver carcinoma was found, with metastases in the periportal and paratracheal lymphatics, the left supraclavicular area, and the pleura.

Proof of radioactivity in the circulating blood is,

perhaps, the key to the fact that Thorotrast deposits were observed in remote metastases.

Three roentgenograms; 7 photomicrographs; 1 photograph. HERBERT C. POLLACK, M.D.
Chicago, Ill.

Radiation Leucopenia in Ankylosing Spondylitis. G. B. Goodman. J. Fac. Radiologists **7:** 167–171, January 1956. (Christie Hospital and Holt Radium Institute, Manchester, England)

This article considers the fall in the white cell count during radiation treatment for ankylosing spondylitis. It was stimulated by the discovery, at the Christie Hospital and Holt Radium Institute, Manchester, of 2 cases of aplastic anemia following the treatment of 848 patients with this disease.

A series of 82 patients was studied. For the spine, long rectangular applicators 7.5 cm. wide were used, with a single rectangular applicator, 15 × 12 cm., for the sacroiliac joints. X-rays were generated at 250 kv, with a half-value layer of 1.63 mm. of copper and a focus-skin distance of 50 cm. For the initial group of patients the weekly dose was 150 r measured on the skin, with back-scatter, but this was later reduced to 100 r. The whole spine was treated, with weekly doses of 100 r and 150 r for ten weeks. Serial blood counts during treatment showed that the proportion of patients with white cell counts below 4,000 per c.m., was significantly greater at the higher dosage level. Analysis of the two dosage groups by age and extent of disease shows trends in each subgroup similar to the differences seen in the group as a whole.

Three cases of blood disorders in patients treated with the higher dosage level are described, 1 of thrombocytopenic purpura, and 2 of aplastic anemia.

[For abstracts of two other papers on the hematologic effects of irradiation of the spine for ankylosing spondylitis, see Radiology **66:** 645, 646, April 1956.—Ed.]

One graph; 3 tables. THEODORE E. KEATS, M.D.
University of California, S. F.

The Action of Ionizing Radiations on Biological Materials. Facts and Theories. J. A. V. Butler. Radiation Res. **4:** 20–32, January 1956. (Chester Beatty Research Institute, London, England)

In this paper the author, a physical chemist, endeavors to give a fairly wide survey of the state of radiobiology from his own point of view. In his opinion, the present stage of radiobiology is one in which there are few new concepts; there is in progress a gathering of information on structure in biological systems which is still far from complete, but which is necessary before new advances can be expected. The basic puzzle of radiology is still unsolved, *i.e.*, the fact that comparatively small doses of radiation produce marked biological changes and, in the case of animals, death, although in general rather large doses of radiation are required to produce observable chemical changes.

The passage of radiation through living tissues obviously initiates a long chain of events—the primary ionizations, the chemical consequences, and the biological events which follow. Although the physical nature of the primary actions has been well worked out, and the chemical consequences have been established at least in numerous simple cases, the link between the chemical changes and the biological consequences is almost completely unknown. The reason for this no doubt has been our ignorance of the structure and organization of the cell. While we have much detailed biochemical information about the working of the various biochemical systems, how their actions are coordinated with each other is largely unknown. It must also be borne in mind that the cell is not a static system; it is a dynamic process, and the effects of the passage of an ionizing particle are determined not only by its immediate action in one place but by its effect on the sequence of events.

Progress in the understanding of radiobiological actions will be rapid when we have a greater knowledge of the actual structural components of cells, and there are indications that radical advances in knowledge of biochemical function are being made, which are relevant to the radiobiological problem.

Eight figures.

Principles and Techniques of Mixed Radiation Dosimetry. Application to Acute Lethality Studies of Mice with the Cyclotron. G. S. Hurst, W. A. Mills, F. P. Conte, and A. C. Upton. Radiation Res. **4:** 49–64, January 1956. (Health Physics Division and Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.)

Because of the increasing use of nuclear machines that subject man to gamma radiations and neutrons, it is important to study the biological effects of various radiations on animals. The common denominator for udging the "amount of radiation" put into the system under observation has been the physical "dose." In their discussion the authors enumerate some of the factors governing the physical dose and elaborate on some of the best methods for measuring them. As an illustration of the application of the principles and technics, a careful study was made of the dose inside an animal exposure facility at the Oak Ridge National Laboratory 86-inch cyclotron. In this experiment, the fast neutron dose as measured with a proportional counter dosimeter and threshold detectors agreed within 10 per cent. Furthermore, the readings of the Failla-Rossi tissue-equivalent chamber, when corrected for gamma-ray response by exposing photographic film in the Bureau of Standards film packet, gave approximately the same neutron dose. A difficulty in making this correction arose from the fact that the gamma-ray film, like all other known gamma-ray dosimeters, has a neutron response which is poorly understood.

The threshold detector method of fast neutron dosimetry has an important advantage over the method in which the dose is measured directly. This advantage is that the dose distribution versus energy obtained from the threshold detector data allows a simple calculation of the distribution of absorbed energy versus linear energy transfer to be made.

A companion paper (Radiation Res. **4:** 117, 1956) describes an acute lethality study on mice, the cyclotron being used as a neutron source.

Seven figures; 4 tables.

Food and Water Consumption of Rats during Exposure to γ-Radiation. J. Garcia, D. J. Kimeldorf, E. L. Hunt, and B. P. Davies. Radiation Res. **4:** 33–41, January 1956. (Division of Biology and Medicine, U. S. Naval Radiological Defense Laboratory, San Francisco, Calif.)

During protracted exposure of rats to low-intensity γ-radiation from a Co^{60} source, a decrease in food and water consumption and also in body weight was ob-

served. The effect was apparent during a single eight-hour exposure to 75 r. The decrease in water consumption became progressively more severe with repeated exposure to radiation. Two of three experiments indicated that food consumption also became altered according to the number of exposures. The decrease in water and food consumption seems to be restricted to the actual period of exposure, since consumption between exposures was at least twice that of sham-irradiated controls. The authors suggest that the changes in food and water intake may be referable to the effects of irradiation upon gastrointestinal function during the period of exposure.

Five figures; 1 table.

The Additivity of γ-Rays and Fission Neutrons in Producing Spleen Weight Reduction. Donn L. Jordan, John W. Clark, and Howard H. Vogel, Jr. Radiation Res. **4**: 77–85, January 1956. (Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Ill.)

In previous work it was found that mixtures of Co^{60} γ-rays and fission neutrons failed to show complete additivity as measured by thirty-day lethality. The authors undertook the present study primarily to test the additivity of these two radiations in producing hematological injury, with spleen weight reduction as the criterion. In addition, they integrated the results of this investigation with previous studies by others on the mouse spleen in order to relate biological effectiveness and linear energy transfer.

Carter (U. S. Atomic Energy Commission Report, AECU-709, 1950) showed that spleen weight decreased progressively from the third to the eighth day after x-irradiation with dosages of 200 to 1,000 r and that the close correlation between weight loss and dose deteriorated after recovery had begun. The present authors found a similar response for fast neutrons. The maximum effect was seen on or near the end of the fifth day; at this time, no recovery process affecting spleen weight was yet apparent. It should be noted that this time-response relationship was investigated for only a limited dose range. It was decided for comparative purposes to use the fifth day, since much previous work had been done at this postirradiation interval.

The per cent spleen weight reduction, five days post-irradiation, is a function of log dose for both Co^{60} γ-rays and fission neutrons for the dose ranges investigated. The neutrons are 4.42 times as effective per unit energy absorbed in producing weight reduction from the 20 per cent through the 80 per cent range. The value at 50 per cent weight reduction is 4.42 ± 0.45.

No departure from additivity could be demonstrated for combined doses of Co^{60} γ-rays and fission neutrons in producing spleen weight reduction. This strengthens the hypothesis that these radiations are additive in producing hematological damage.

This investigation, combined with others using splenic regression as a criterion, shows that biological effectiveness per unit energy absorbed increases for radiations dissipating from 0.3 to 30 kev/μ of path.

Five figures; 1 table.

Suggested Procedure for Performance of Autopsies Containing Radioactive Iodine. Russell F. Cowing and Egilda DeAmicis. Am. J. Clin. Path. **26**: 29–35, January 1956.

With the increasing use of radioisotopes in medical treatment have come the associated problems of protecting pathologists performing autopsies on radioactive bodies (New England J. Med. **251**: 380, Sept. 2, 1954. Abst. in Radiology **65**: 319, 1955). The present paper deals with procedures for performance of autopsies on cadavers containing radioiodine, I^{131}. It is based on the authors' own experience, talks with pathologists, and on information relating to radiation exposure contained in the National Bureau of Standards Handbook No. 56, entitled "Safe Handling of Cadavers Containing Radioactive Isotopes."

The permissible working time varies with such factors as dose and interval between treatment and autopsy. Instruments giving a thyroid-to-hand distance of at least 10 cm. should be used for exposure and dissection of the gland and adjacent parathyroids. The wearing of two pairs of surgical gloves is recommended. Similar precautions should be observed in handling metastatic deposits.

Thermal Neutron Equivalence of Whole-Body X-Irradiation. L. F. Nims and L. Lewis. Radiation Res. **4**: 42–48, January 1956. (Biology Department and the Health Physics Division of the Brookhaven National Laboratory, Upton, L. I., New York)

Young rats, after sublethal exposures to whole-body x-rays or thermal neutrons, temporarily lose weight and then begin to gain again at an apparently normal rate. The period of time, designated as growth delay, for irradiated animals to reach again their weight of the day of irradiation has been found to be a straight-line function of the x-ray dose over the range of 0 to 600 r or so (Am. J. Physiol. **171**: 17, 1952. Abst. in Radiology **61**: 311, 1953). In the experiments described here the utility of growth delay in the determination of the thermal neutron equivalence to whole-body x-irradiation was tested.

For the main objective of the investigation male and female rats were exposed to x-rays or to thermal neutrons. The total doses the rats received were distributed in the high and low dose regions so that an accurate determination of the slopes of the regression lines could be made. The thermal column irradiations consisted principally of twenty- and ninety-minute exposures in a thermal neutron flux of approximately 9×10^8 n/cm²/sec., and the total gamma-ray dose rate was 215 r/hr. The x-ray exposures were made up of 100-r and 550-r doses delivered at 150 r/min. The differences in dose rate between the neutron and x-ray exposures are not great enough to influence the response significantly. The data from the rats exposed in the thermal column were corrected for the gamma-ray effect by assuming that the total gamma-ray dose received was 0.6 times as effective in producing growth delay as an equal quantity of x-rays.

The thermal neutron flux equivalent to 1 r of x-rays for the biological end point of growth delay was found to be 0.79×10^{10} n/cm.²